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See application file for complete search history.(56) **References Cited**

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Primary Examiner — Niloofar Rahmani(74) *Attorney, Agent, or Firm* — Markus Bergauer(57) **ABSTRACT**

The present disclosure provides crystalline and amorphous forms of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, including several anhydrous, hydrate and solvate forms, and solid state forms thereof, pharmaceutical compositions, and methods of treating a disease mediated by KRAS G12C inhibition.

16 Claims, 33 Drawing Sheets

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FIG. 1

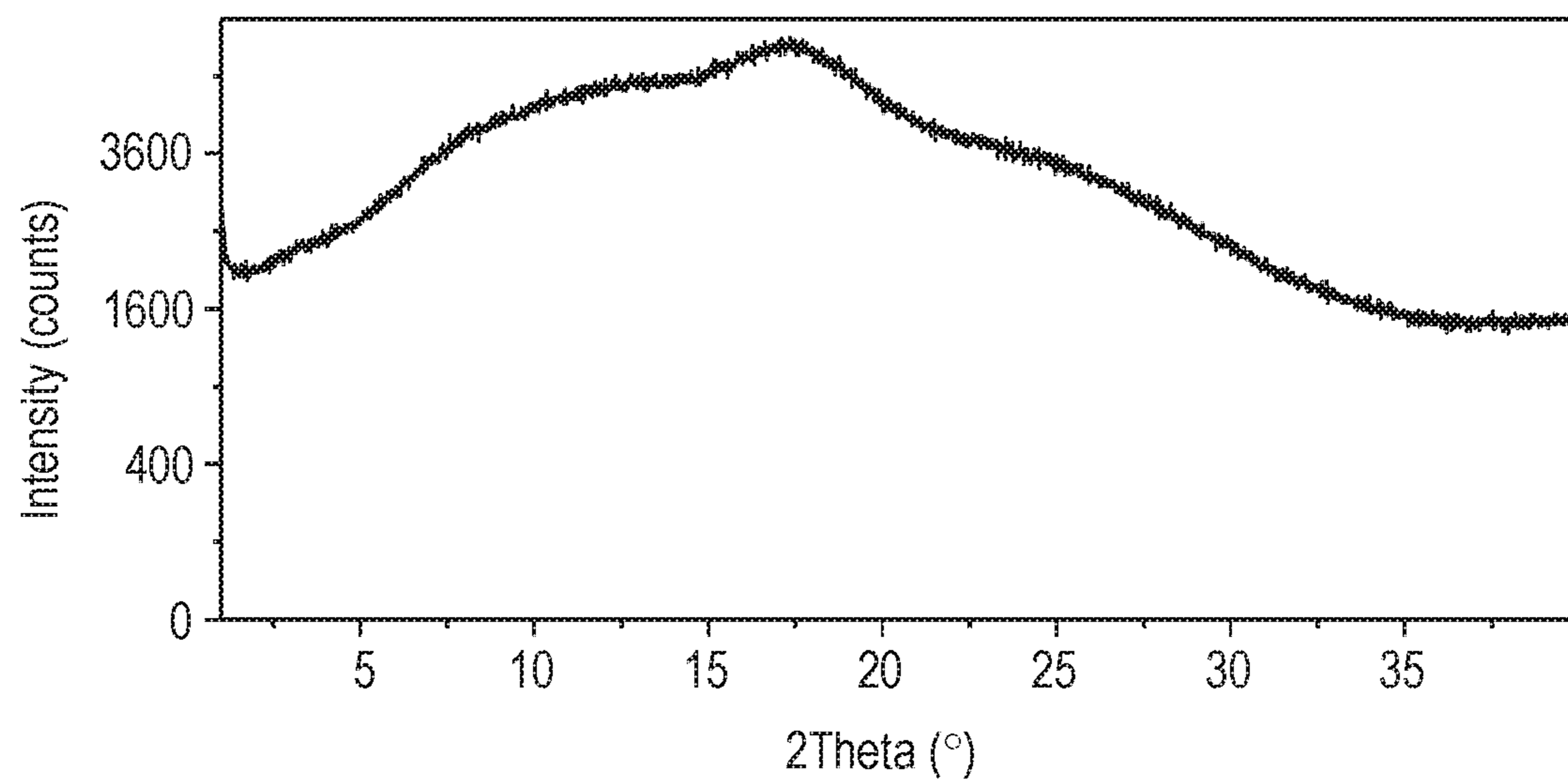


FIG. 2

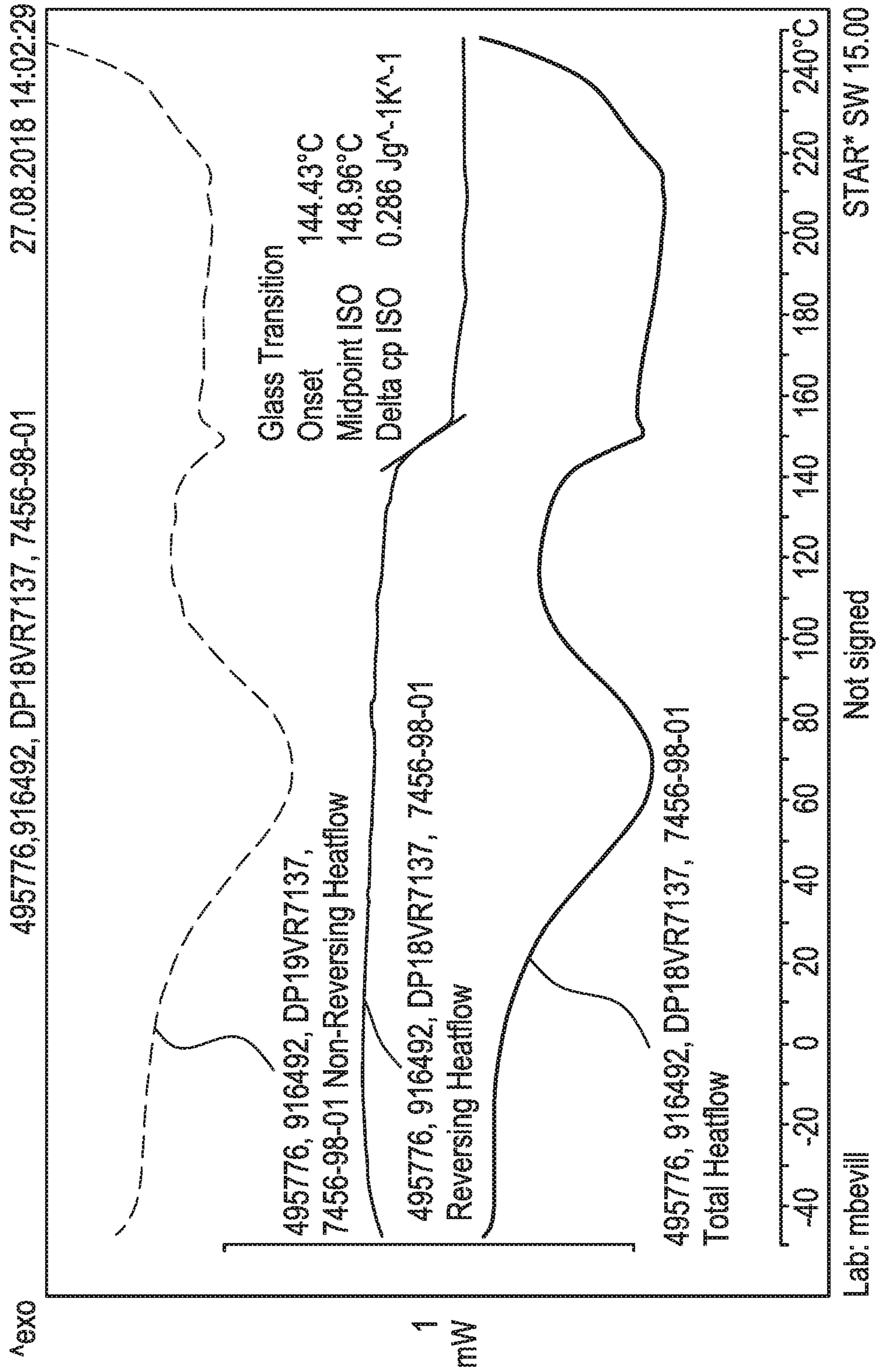


FIG. 3

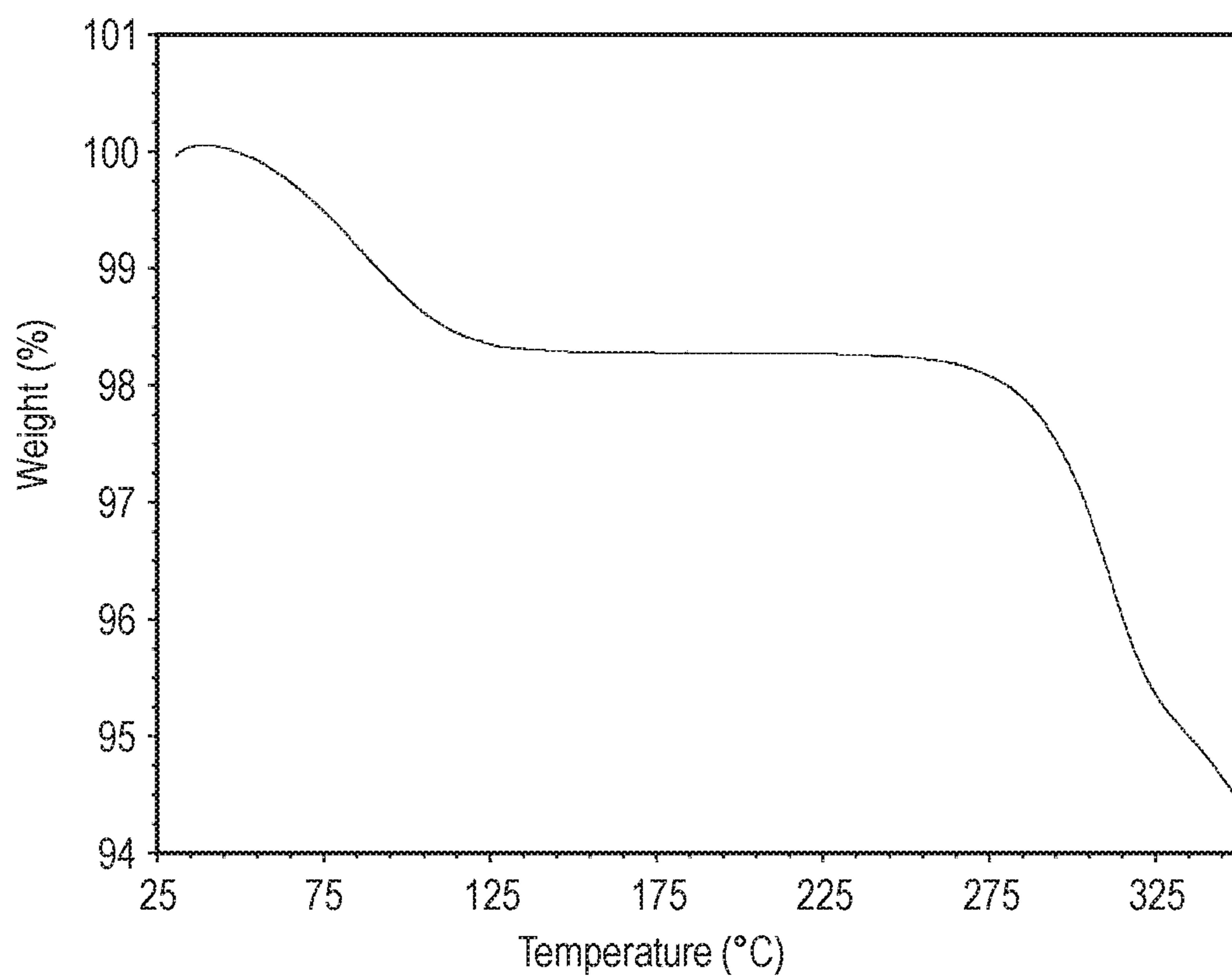


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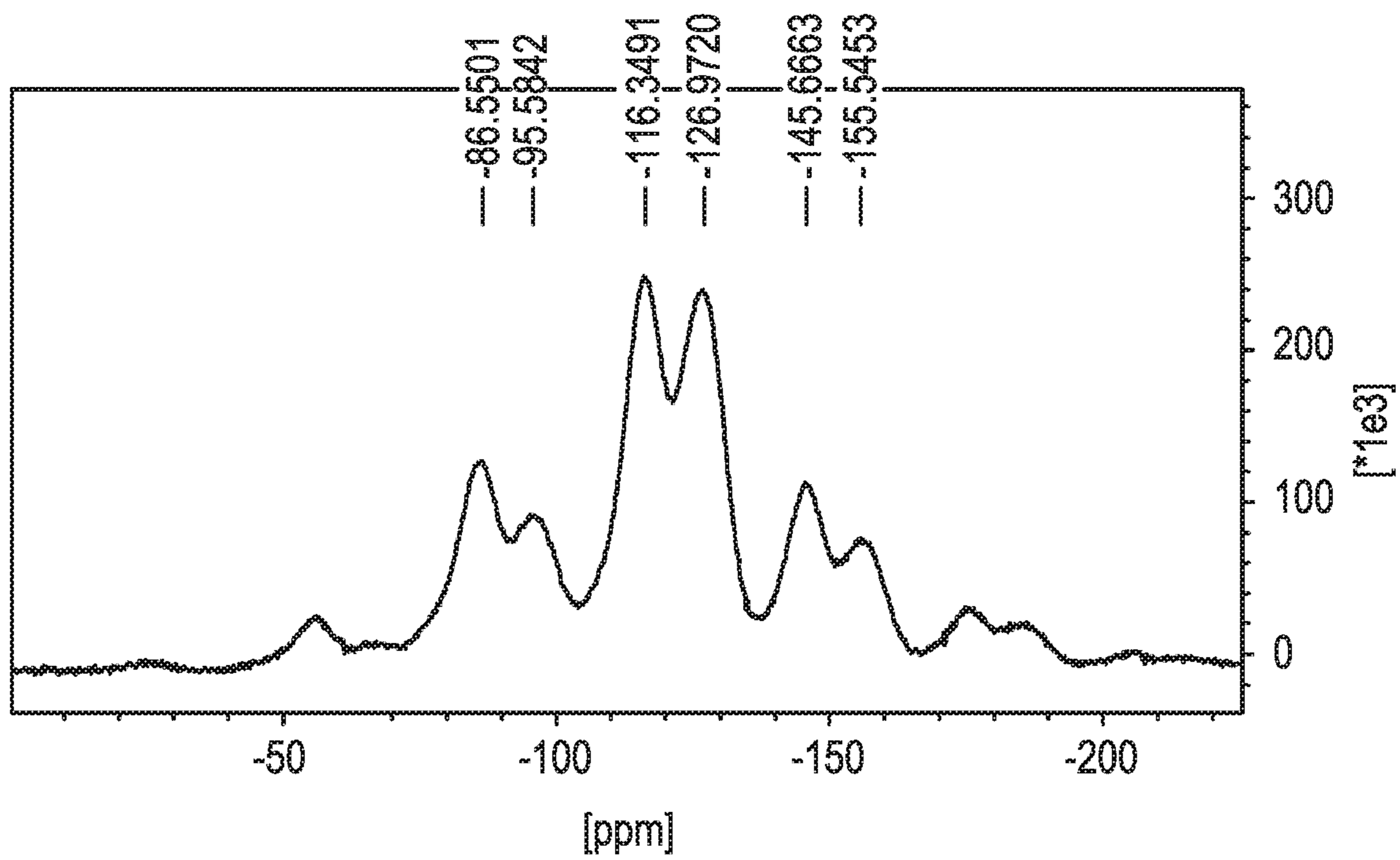


FIG. 5

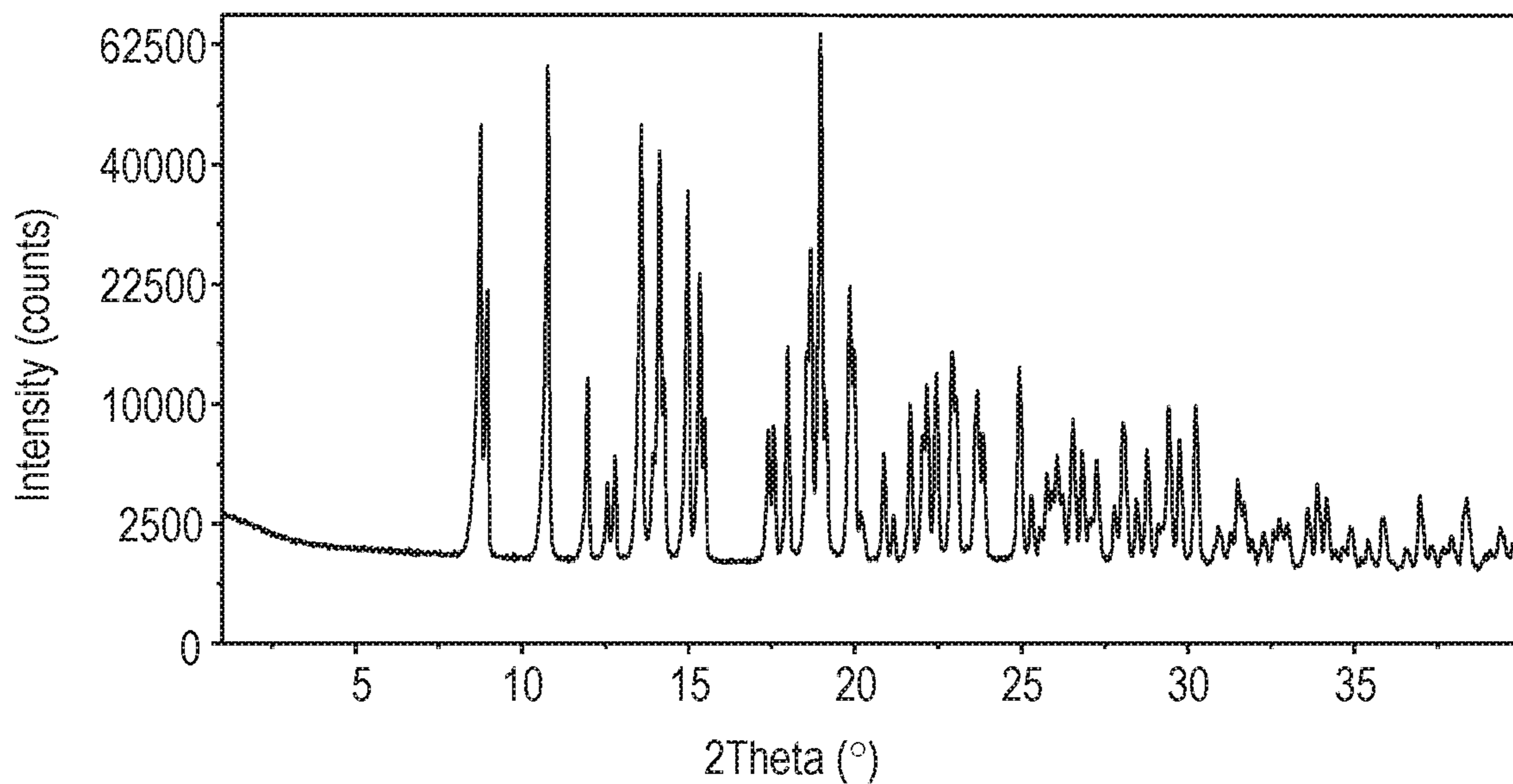


FIG. 6

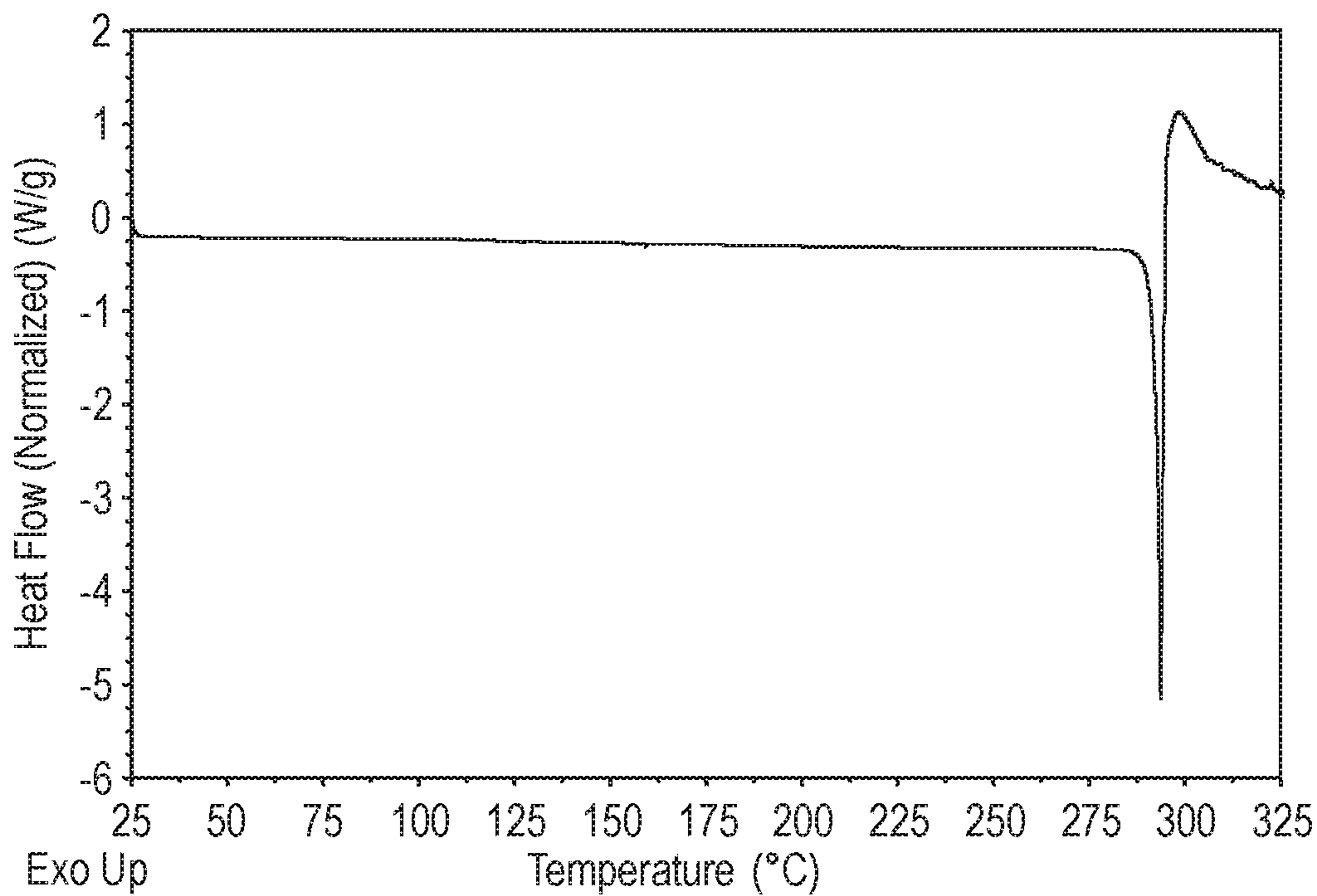
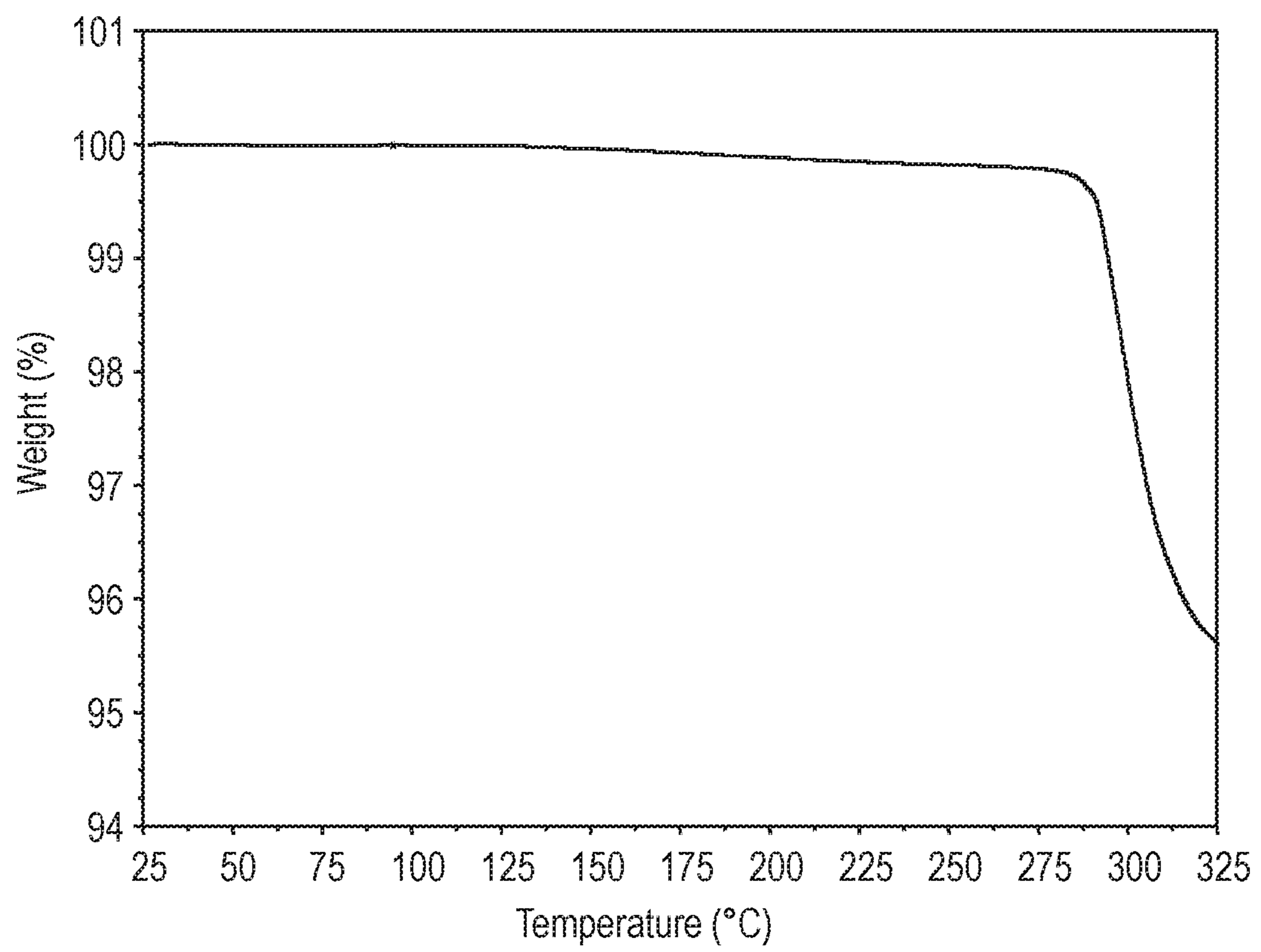


FIG. 7



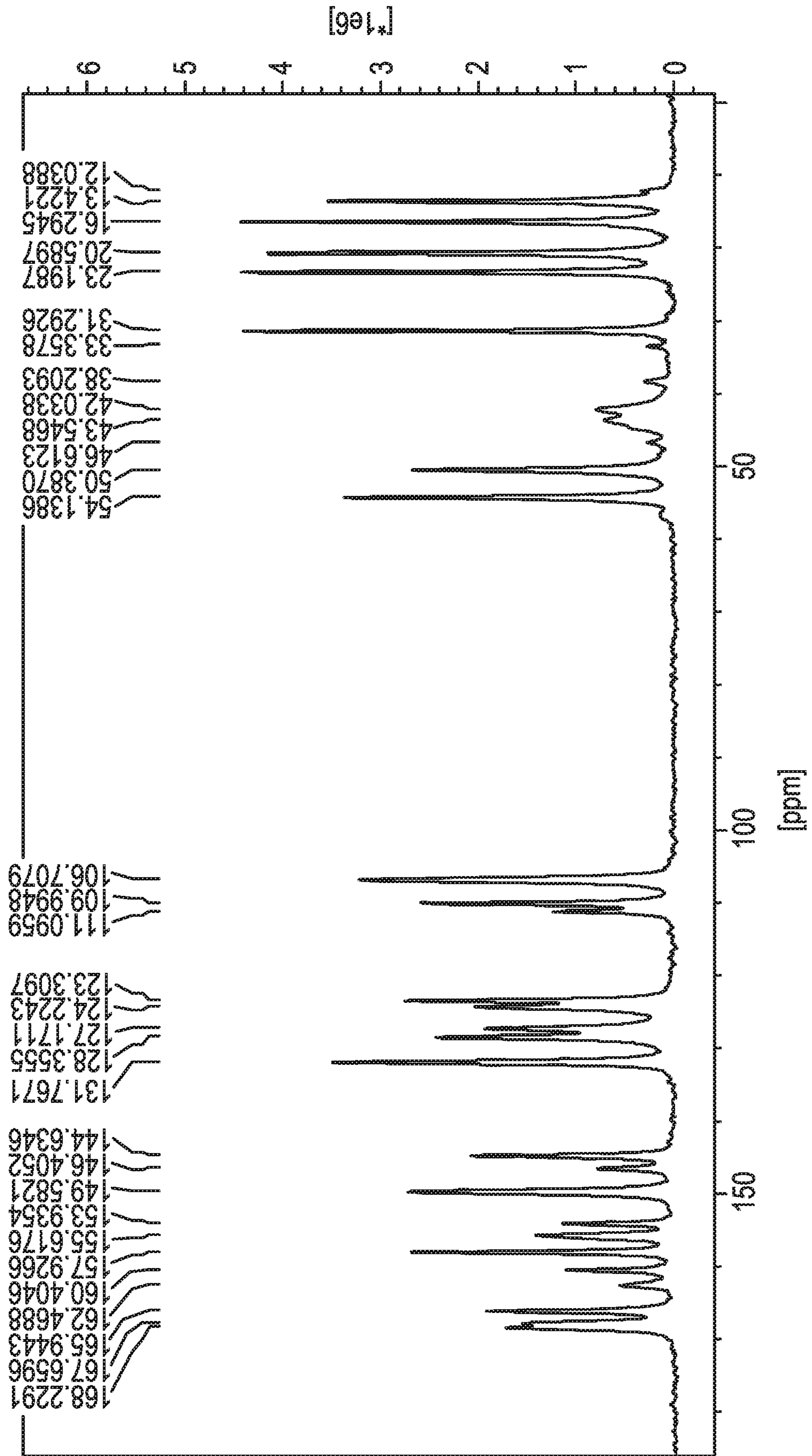


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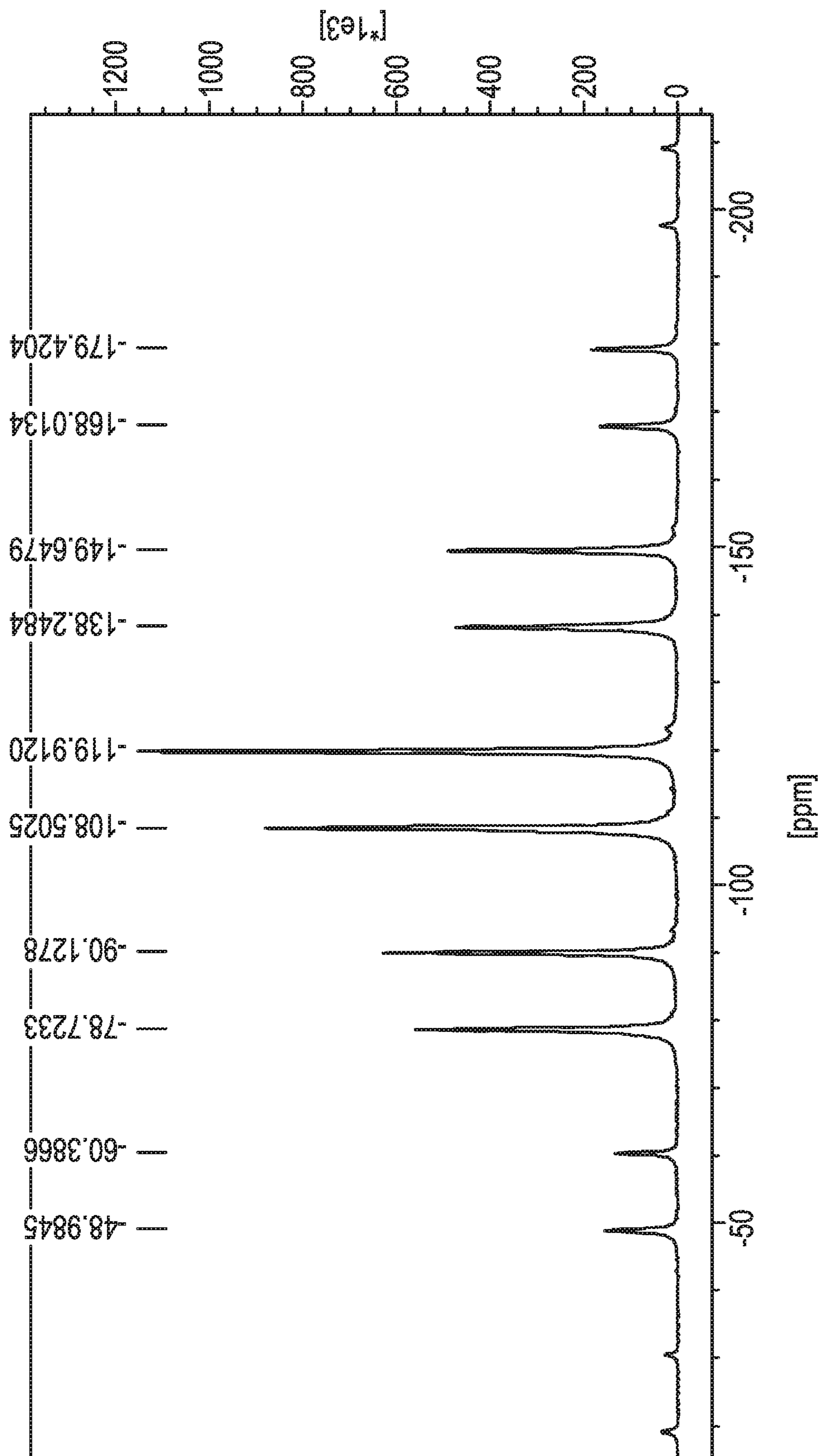


FIG. 9

FIG. 10

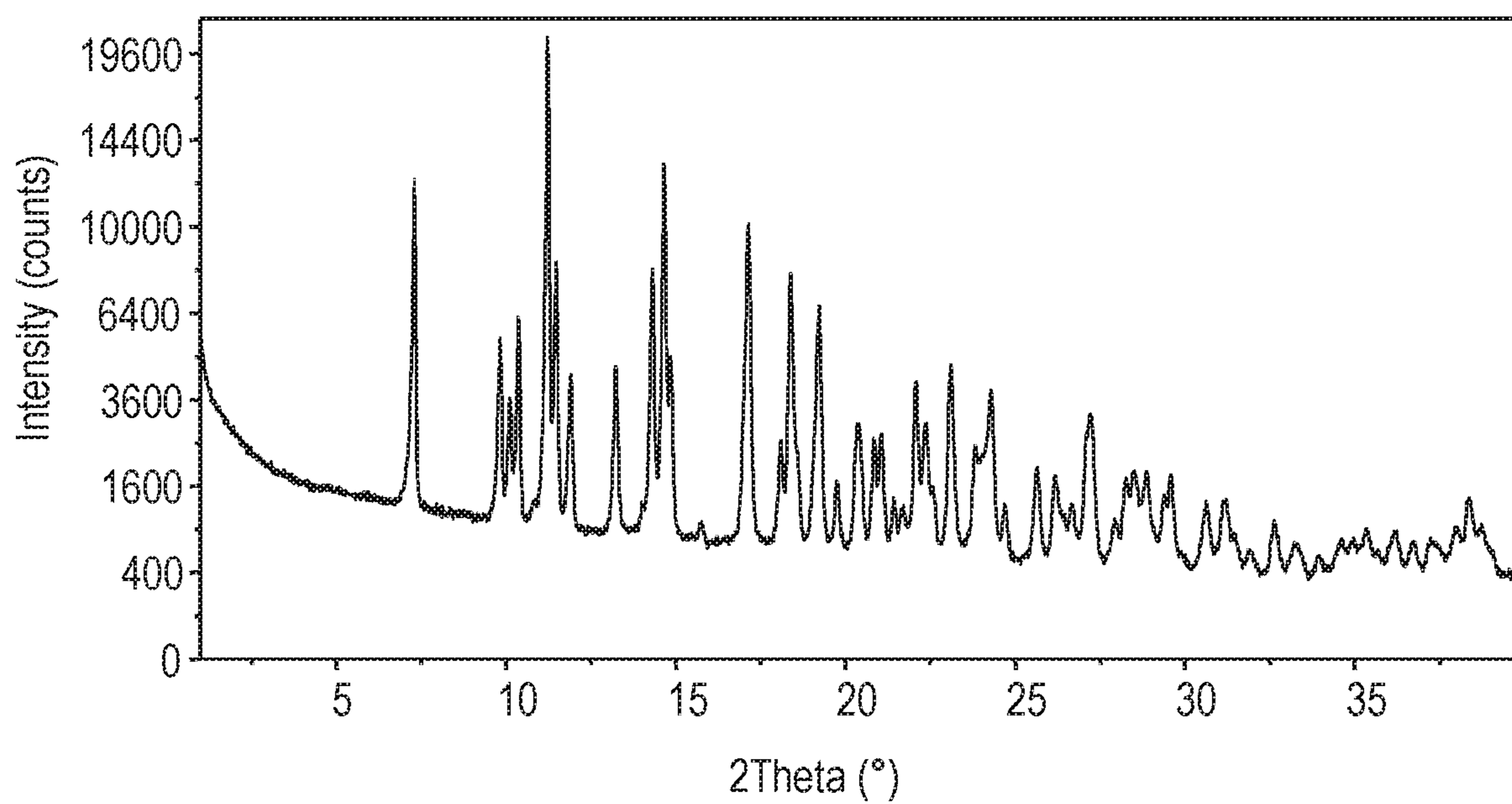


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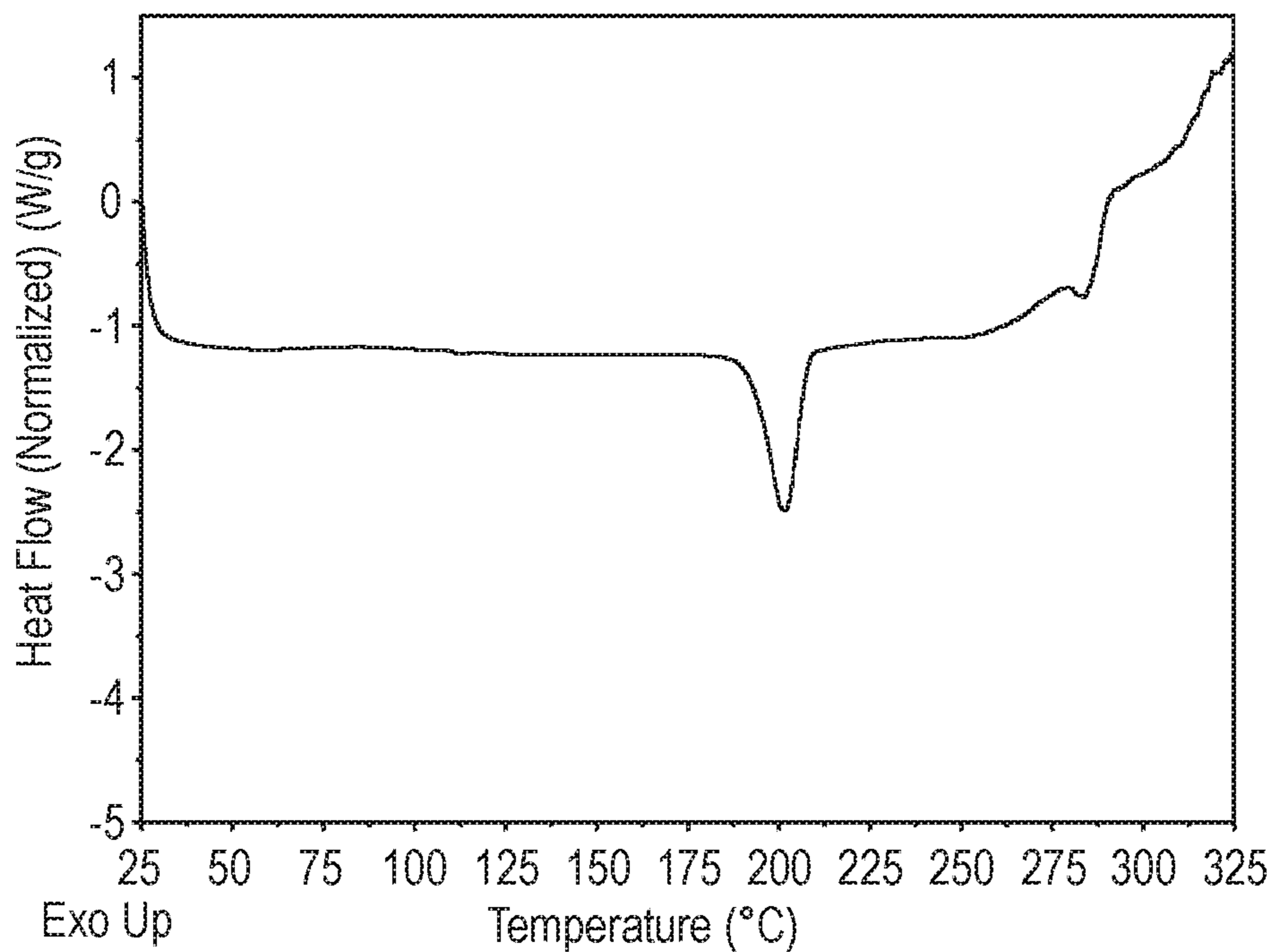
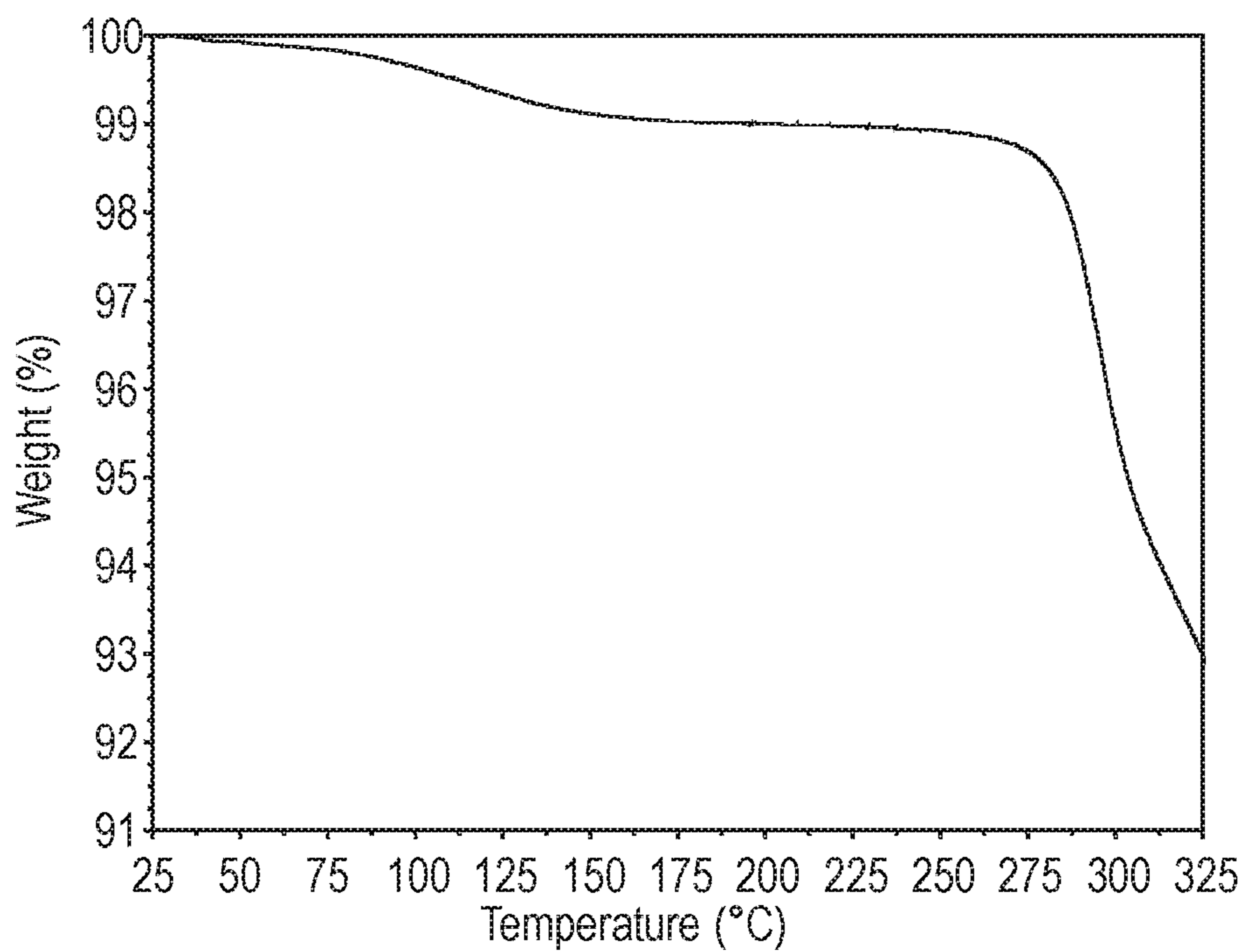


FIG. 12



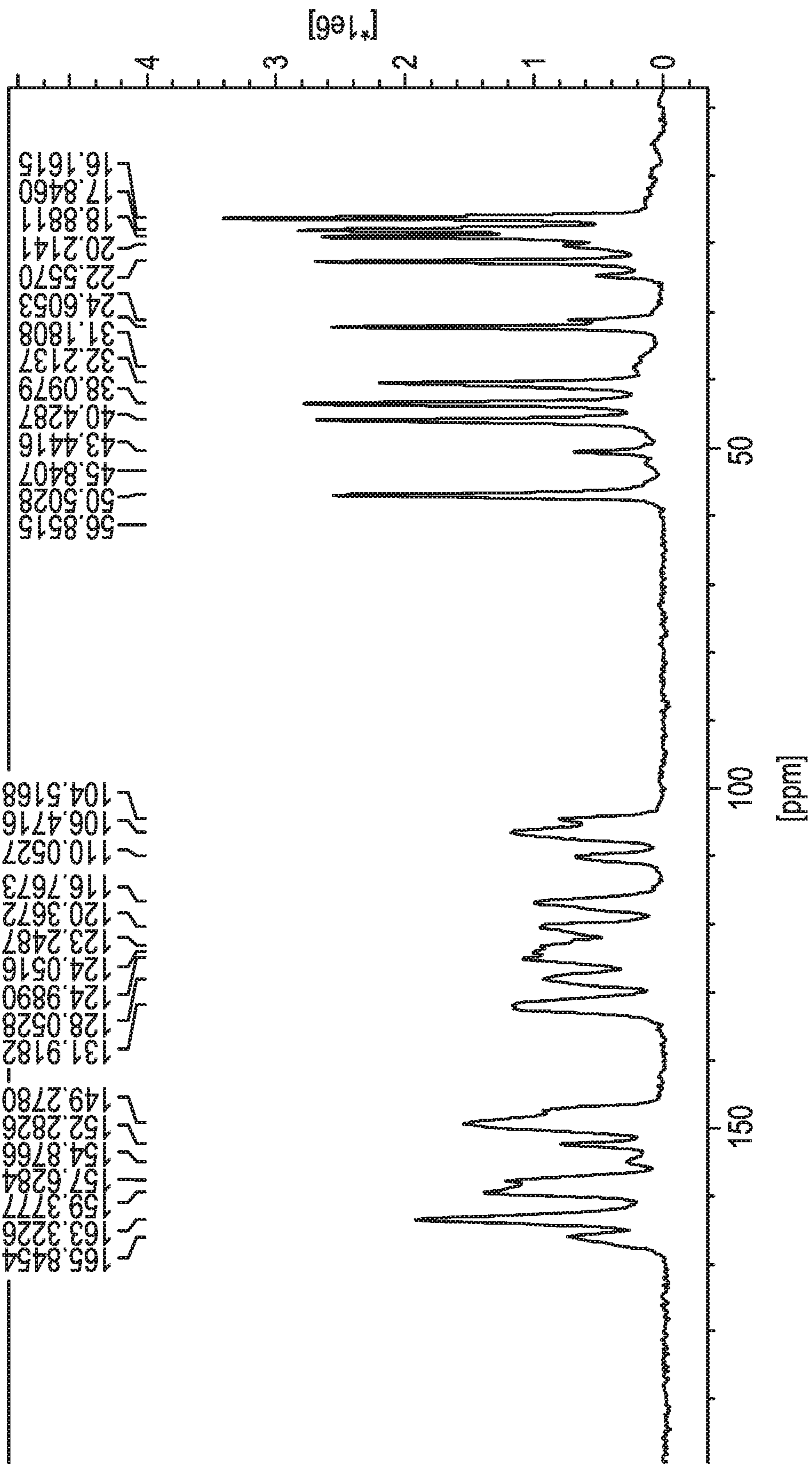


FIG. 13

FIG. 14

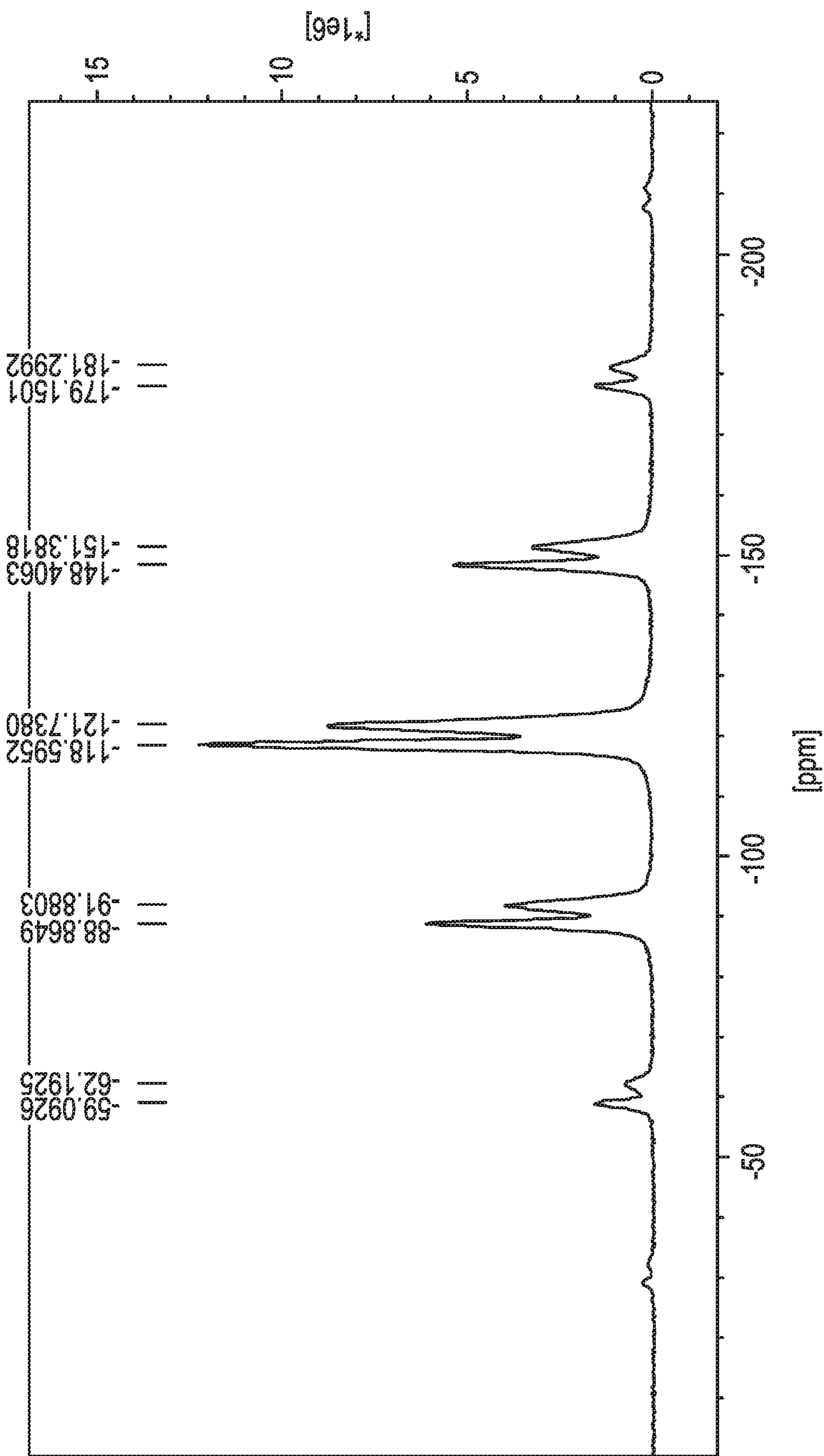


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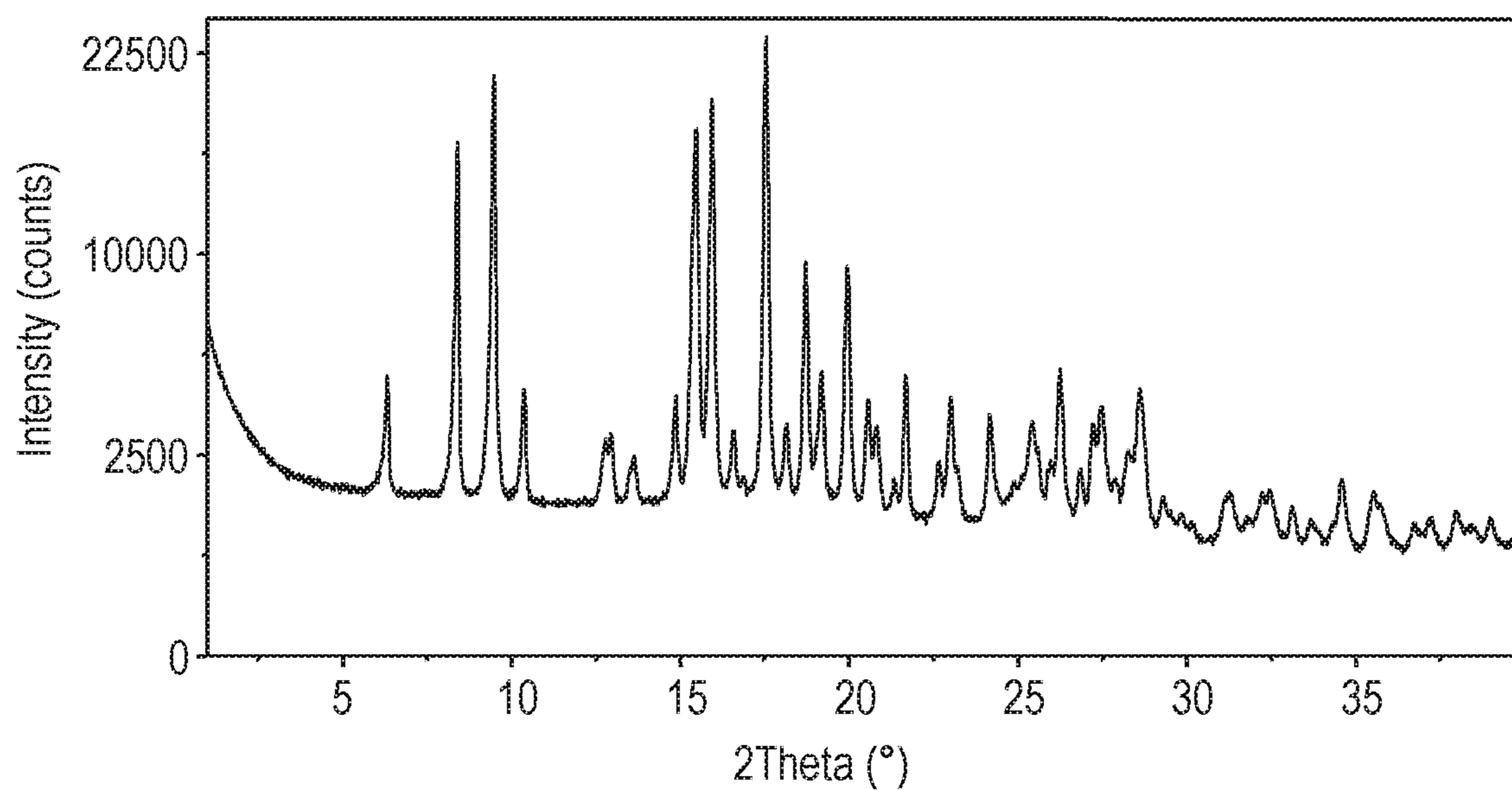


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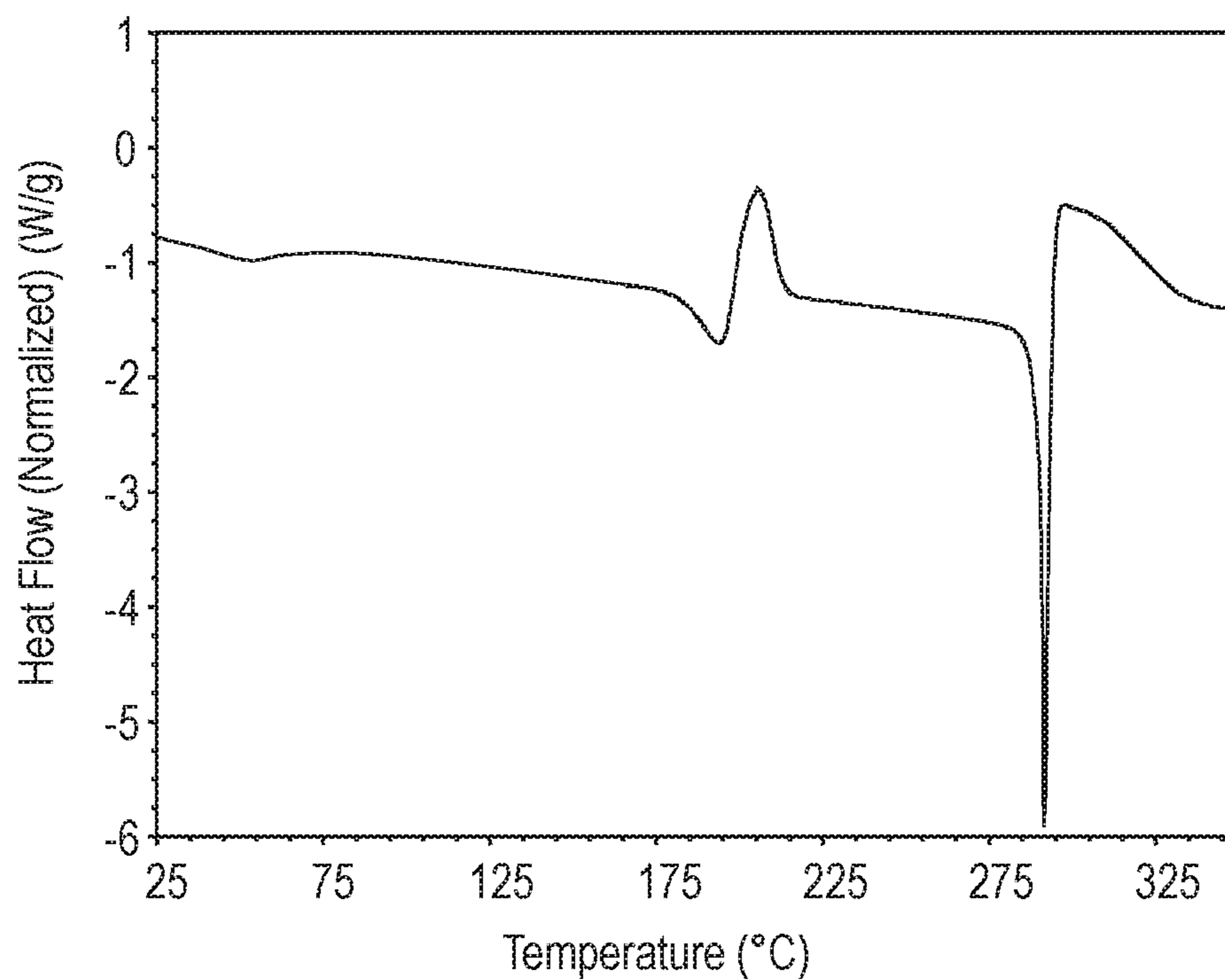


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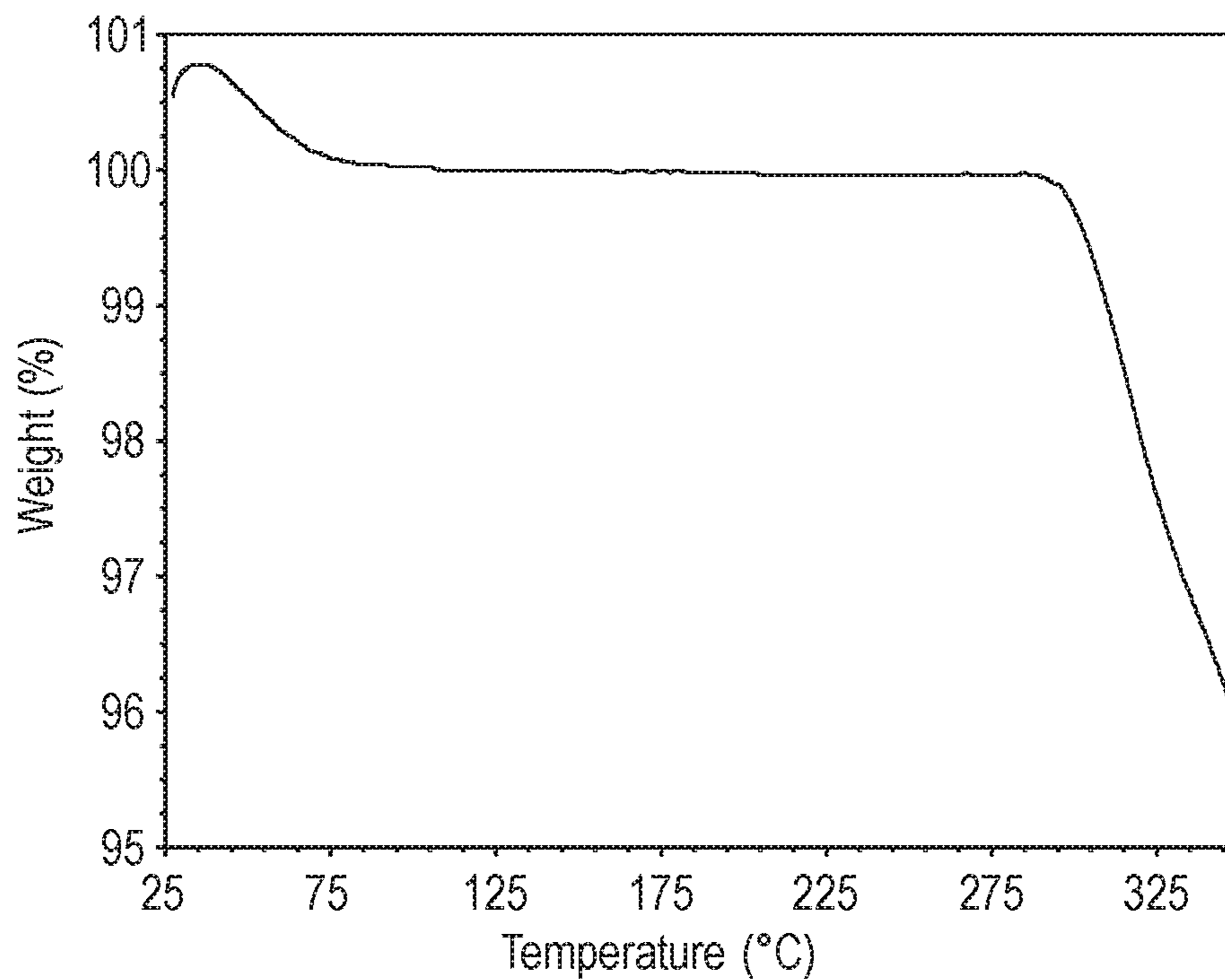


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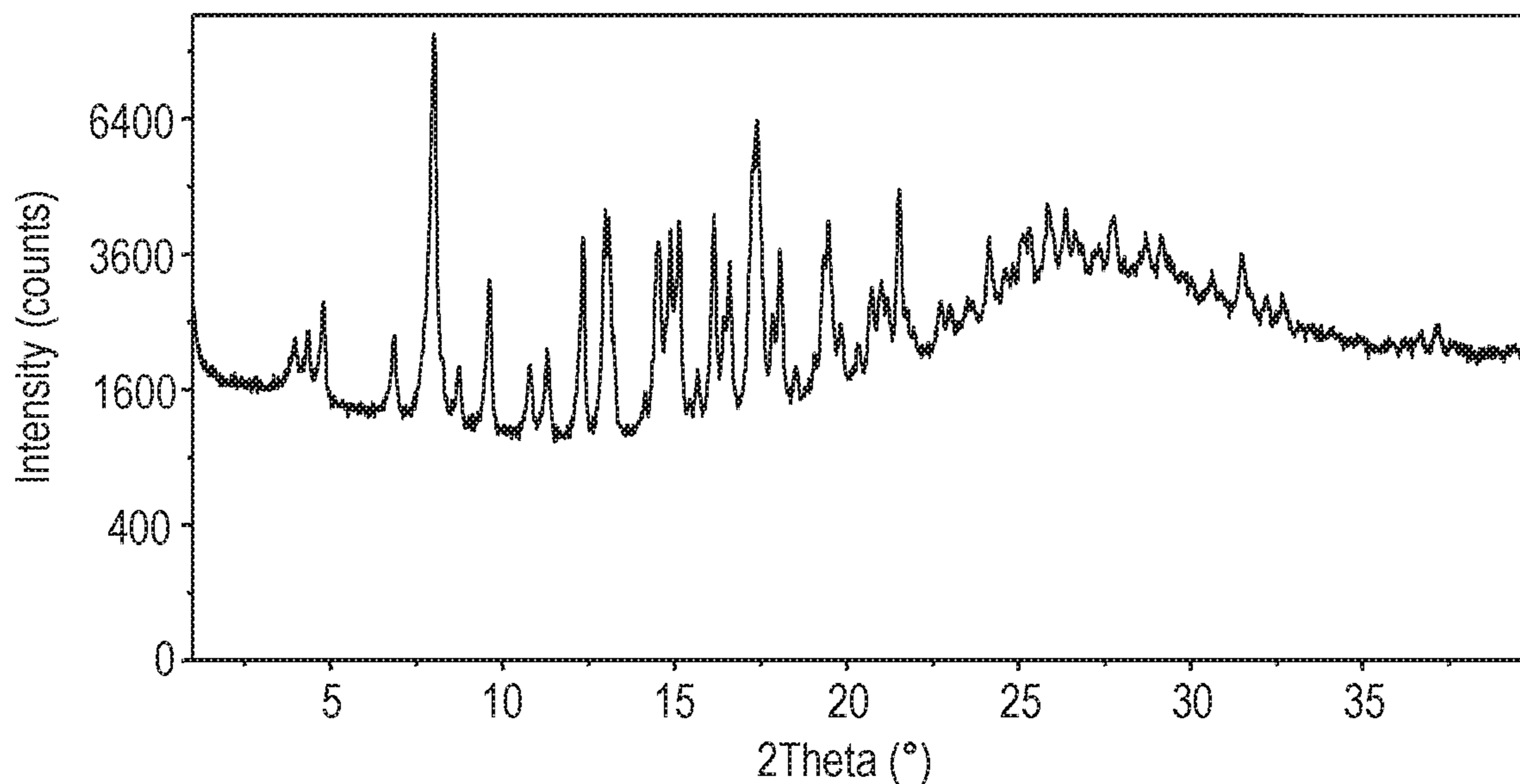


FIG. 19

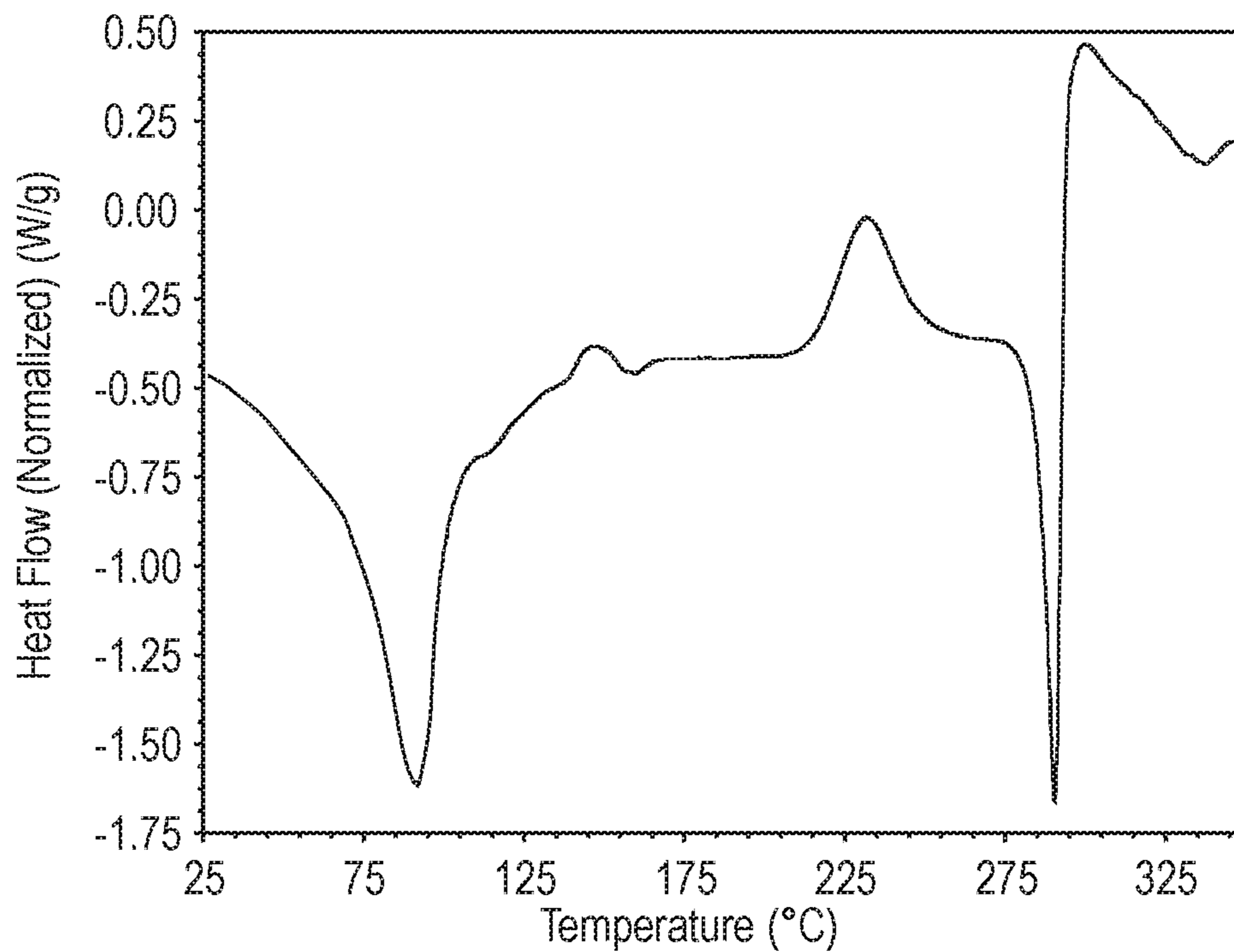


FIG. 20

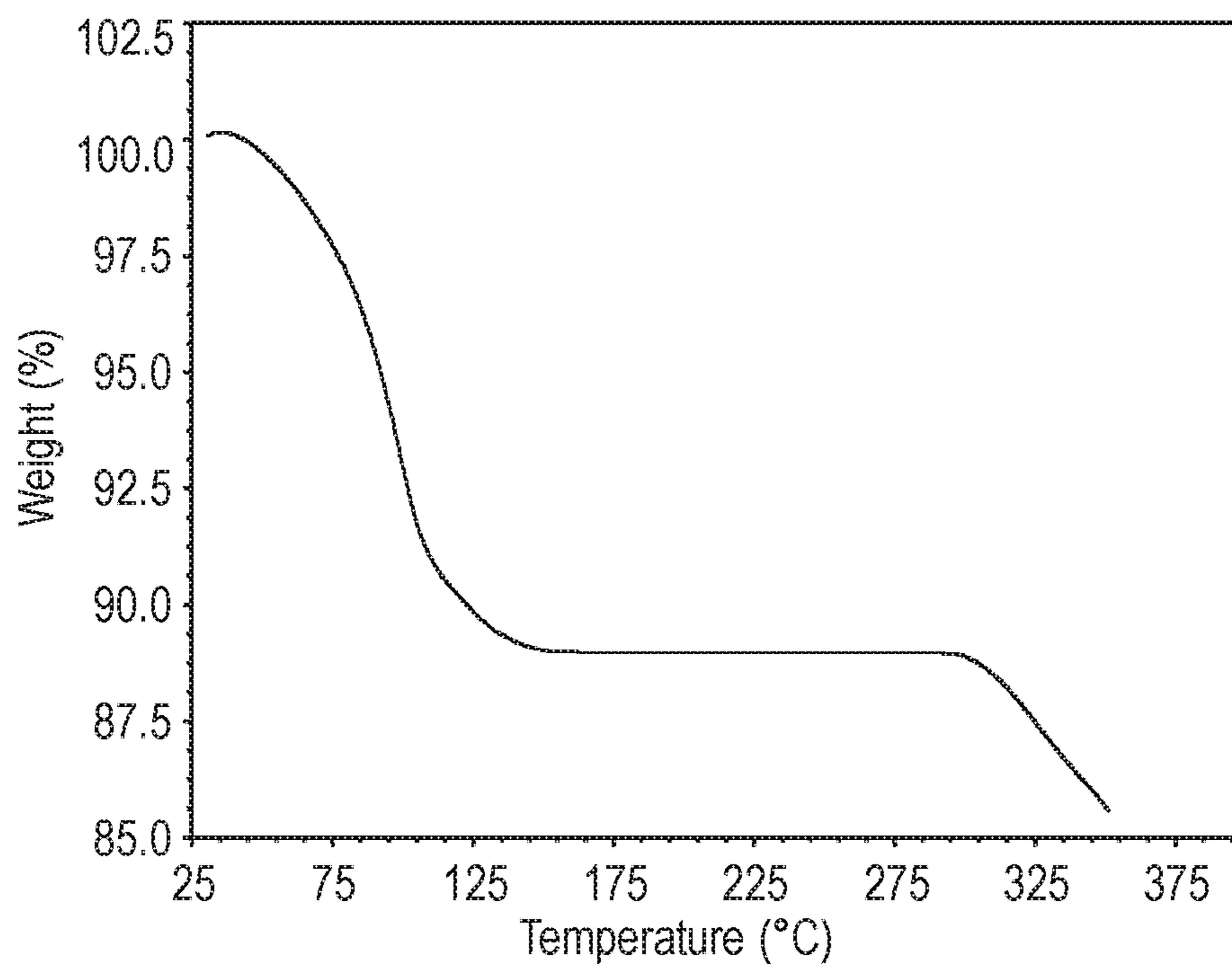


FIG. 21

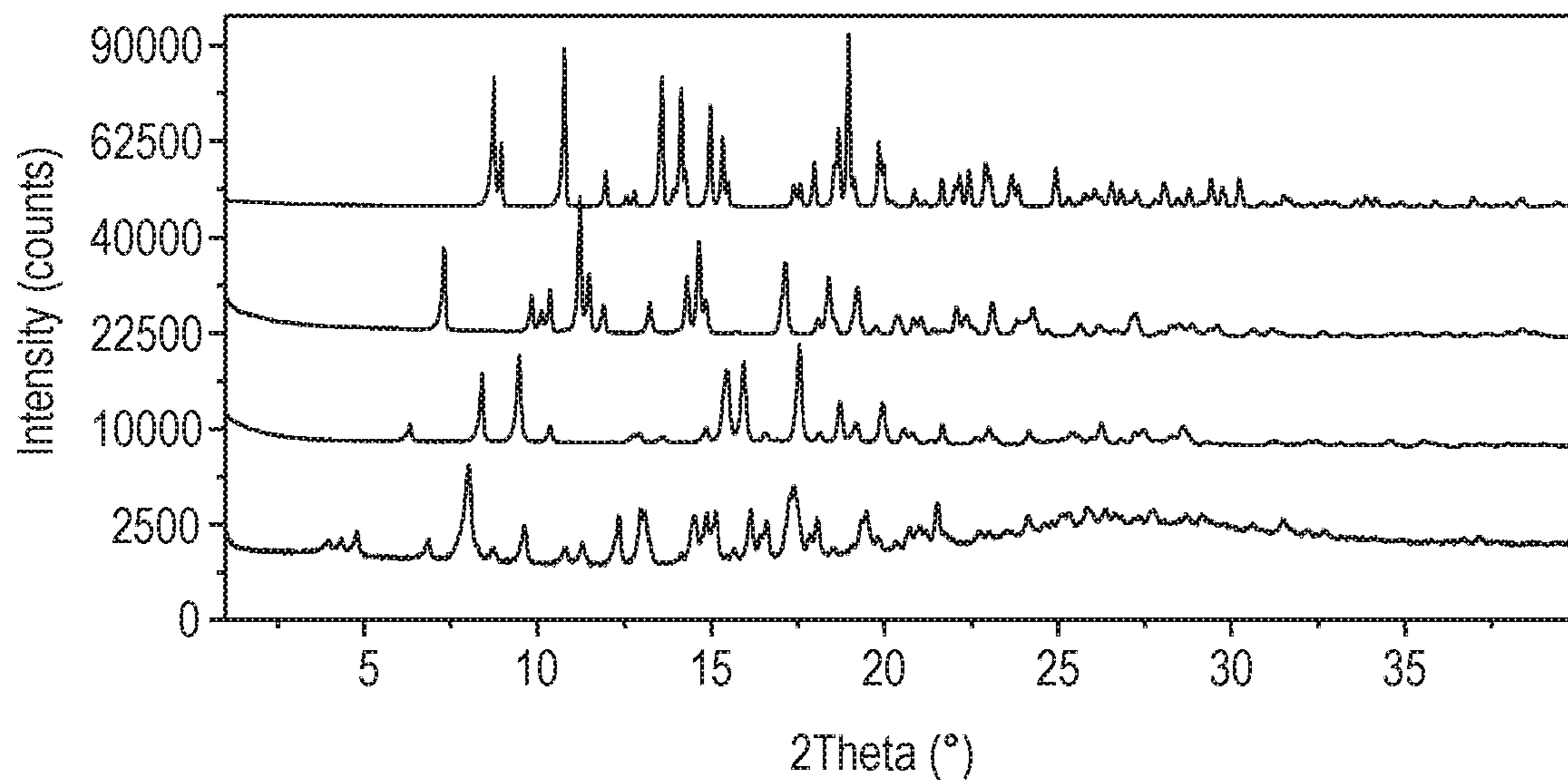


FIG. 22

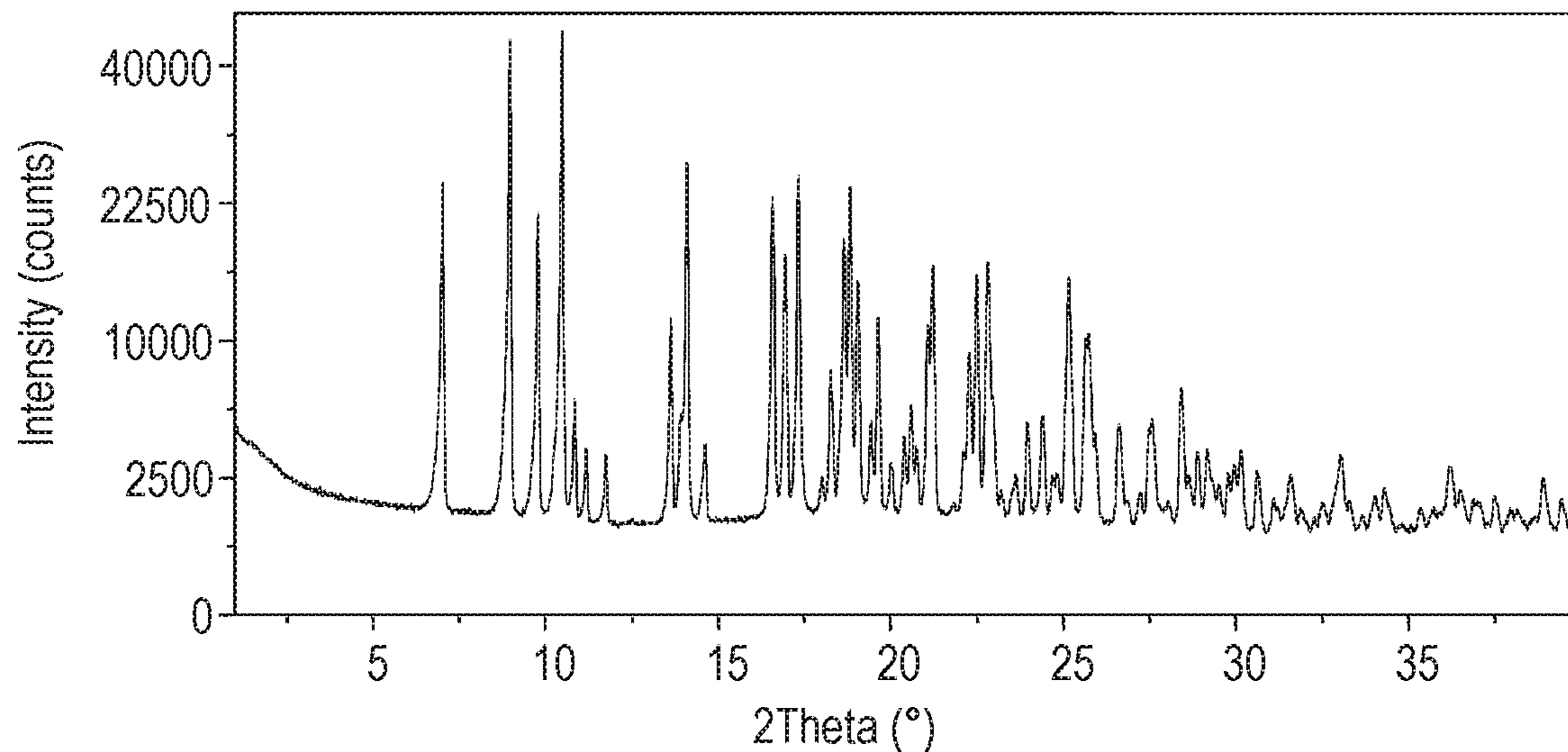


FIG. 23

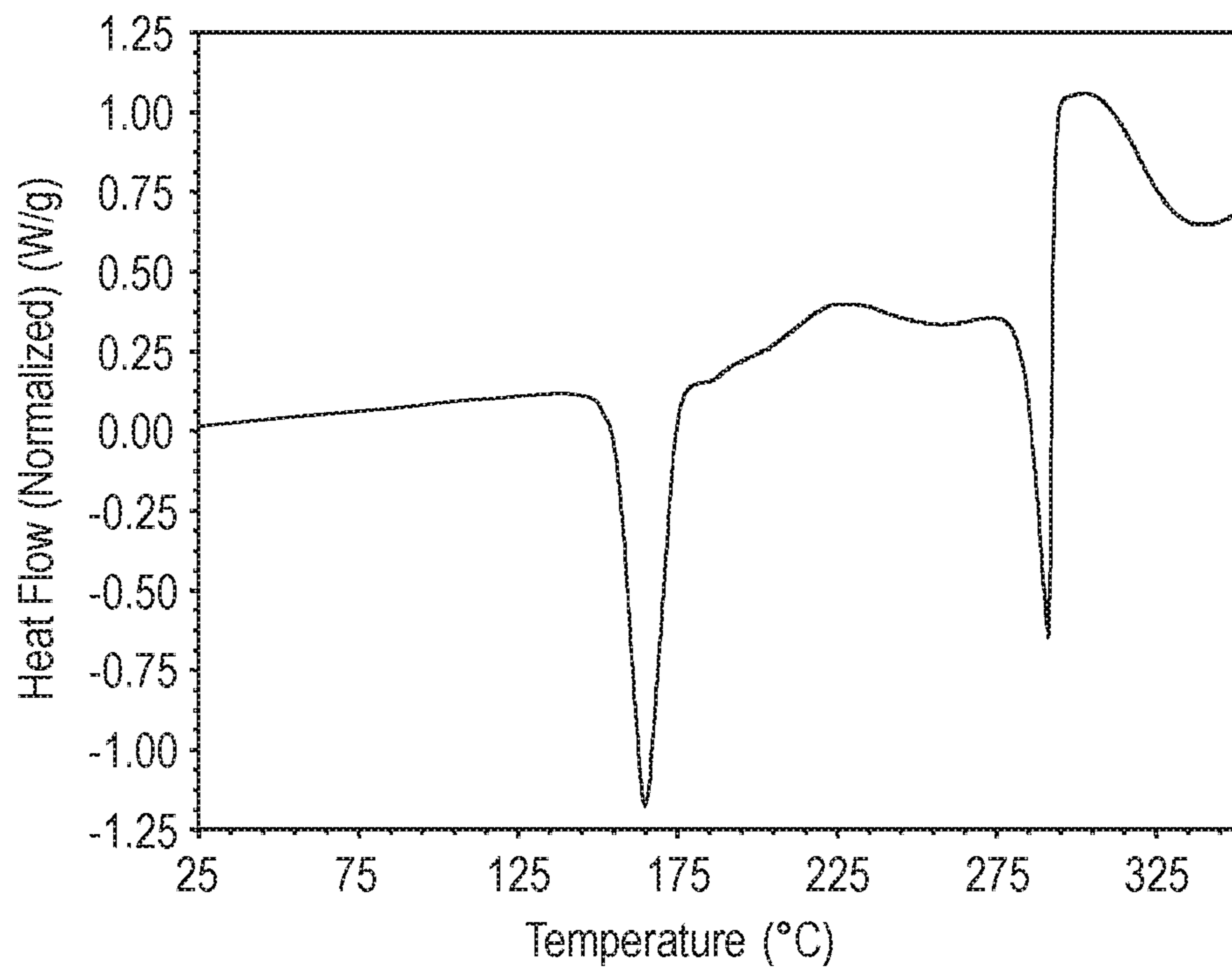


FIG. 24

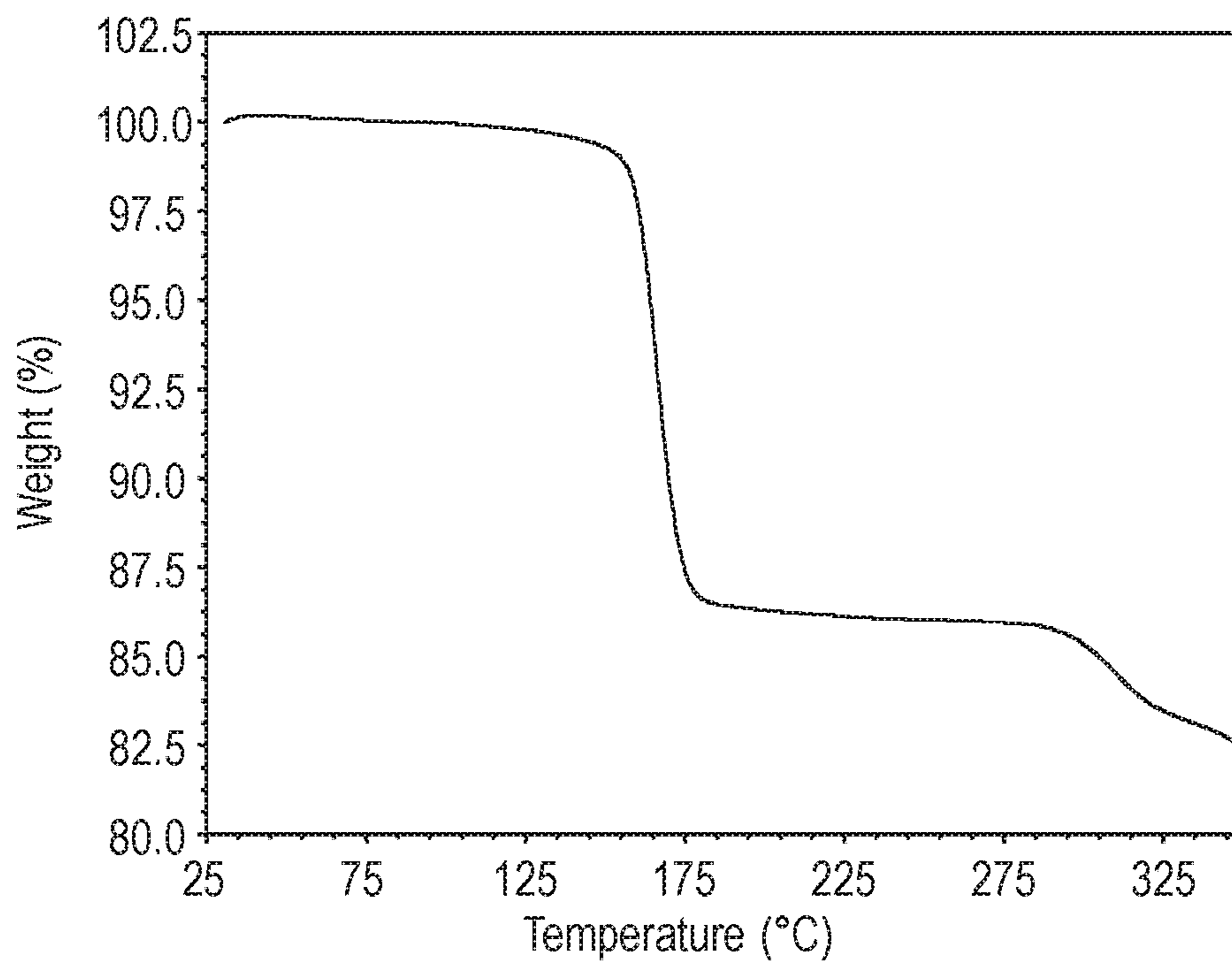


FIG. 25

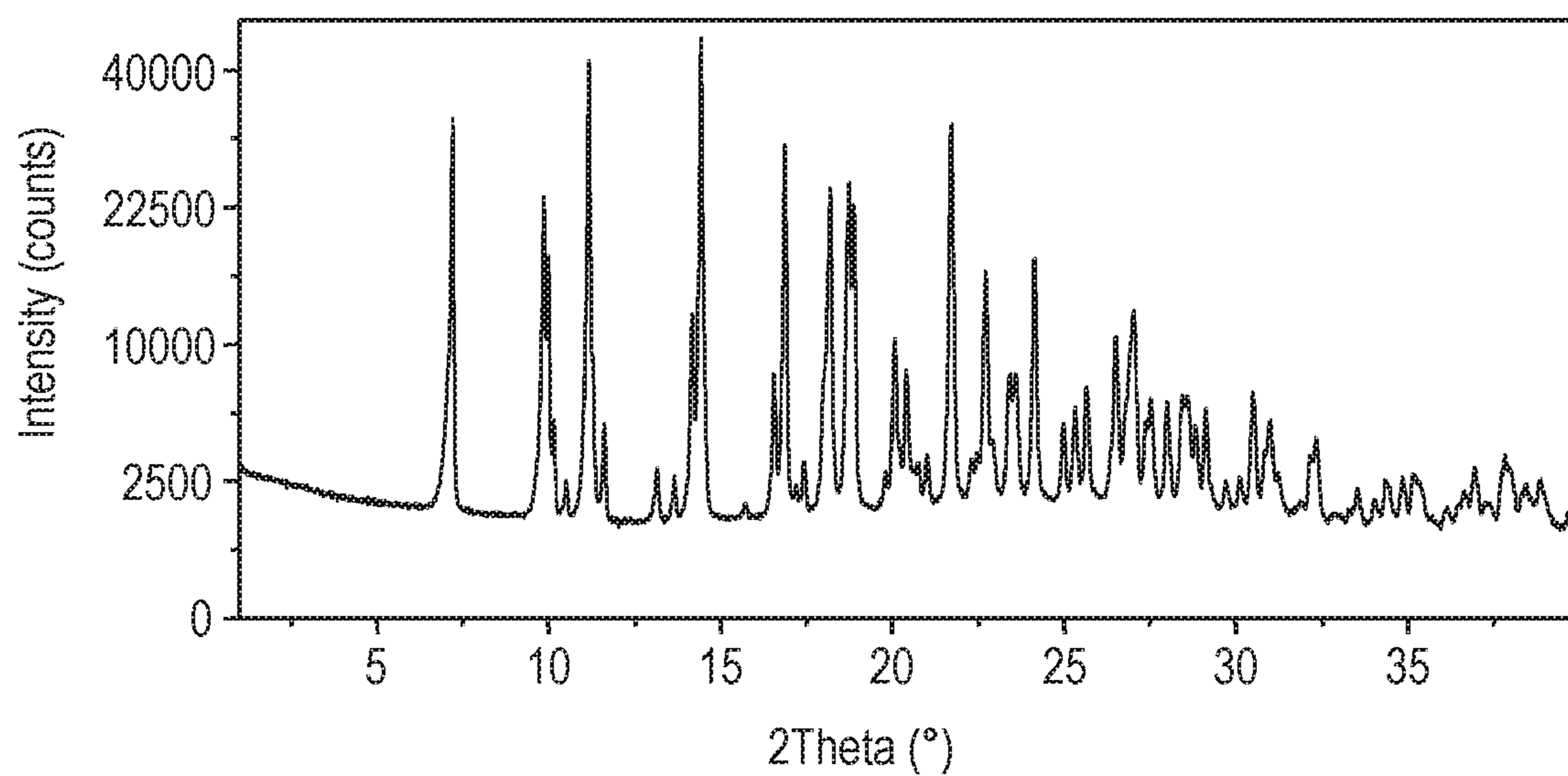


FIG. 26

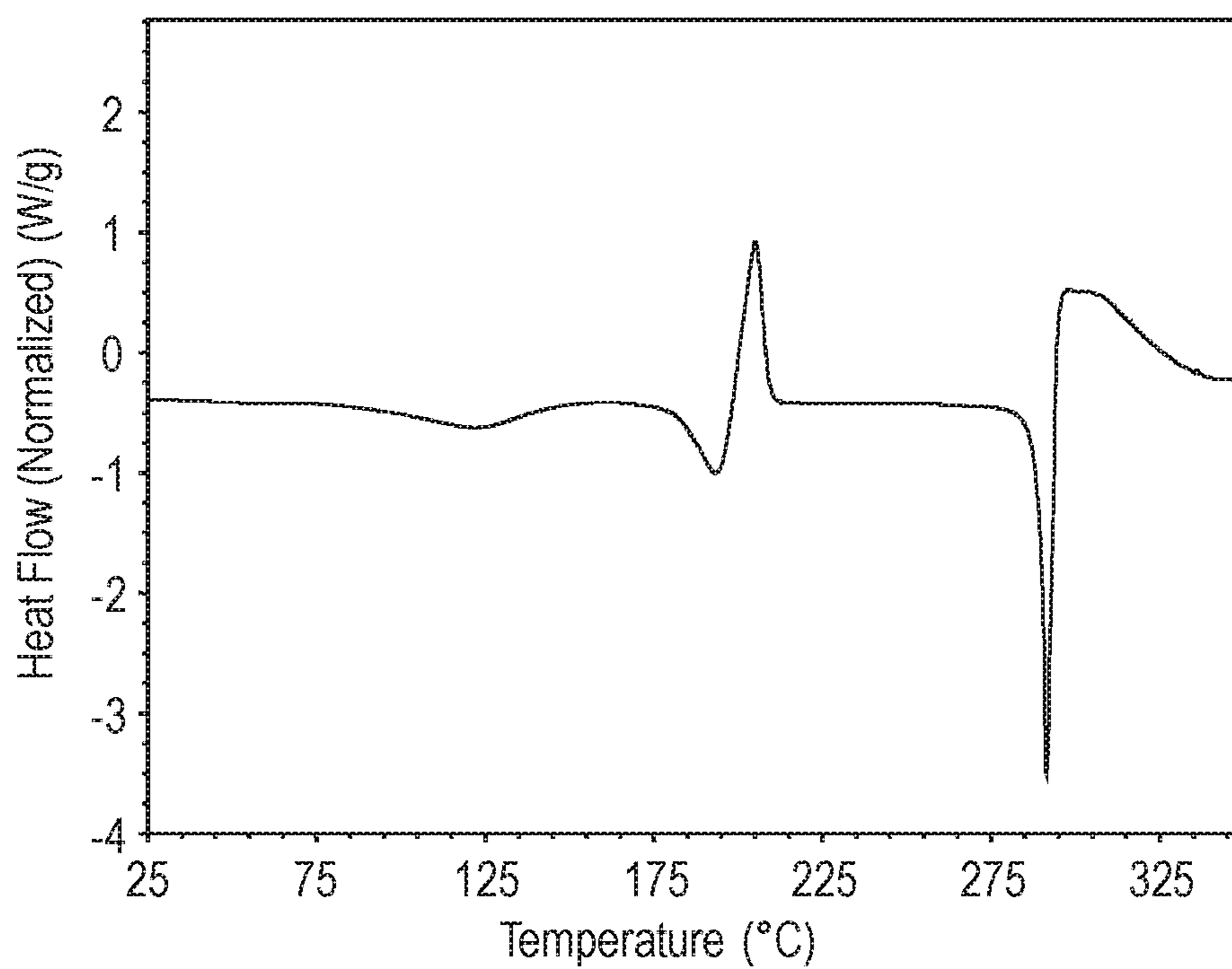


FIG. 27

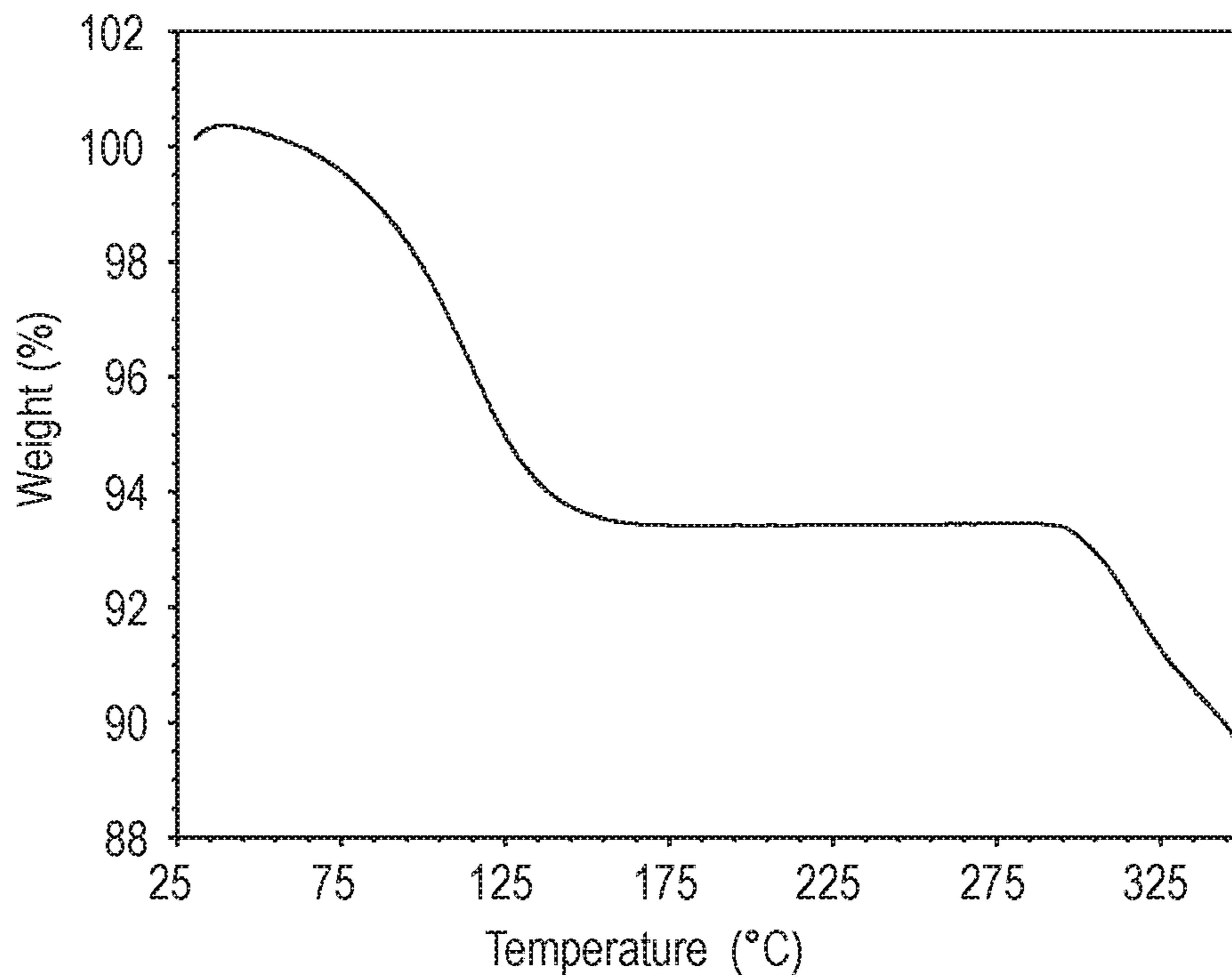


FIG. 28

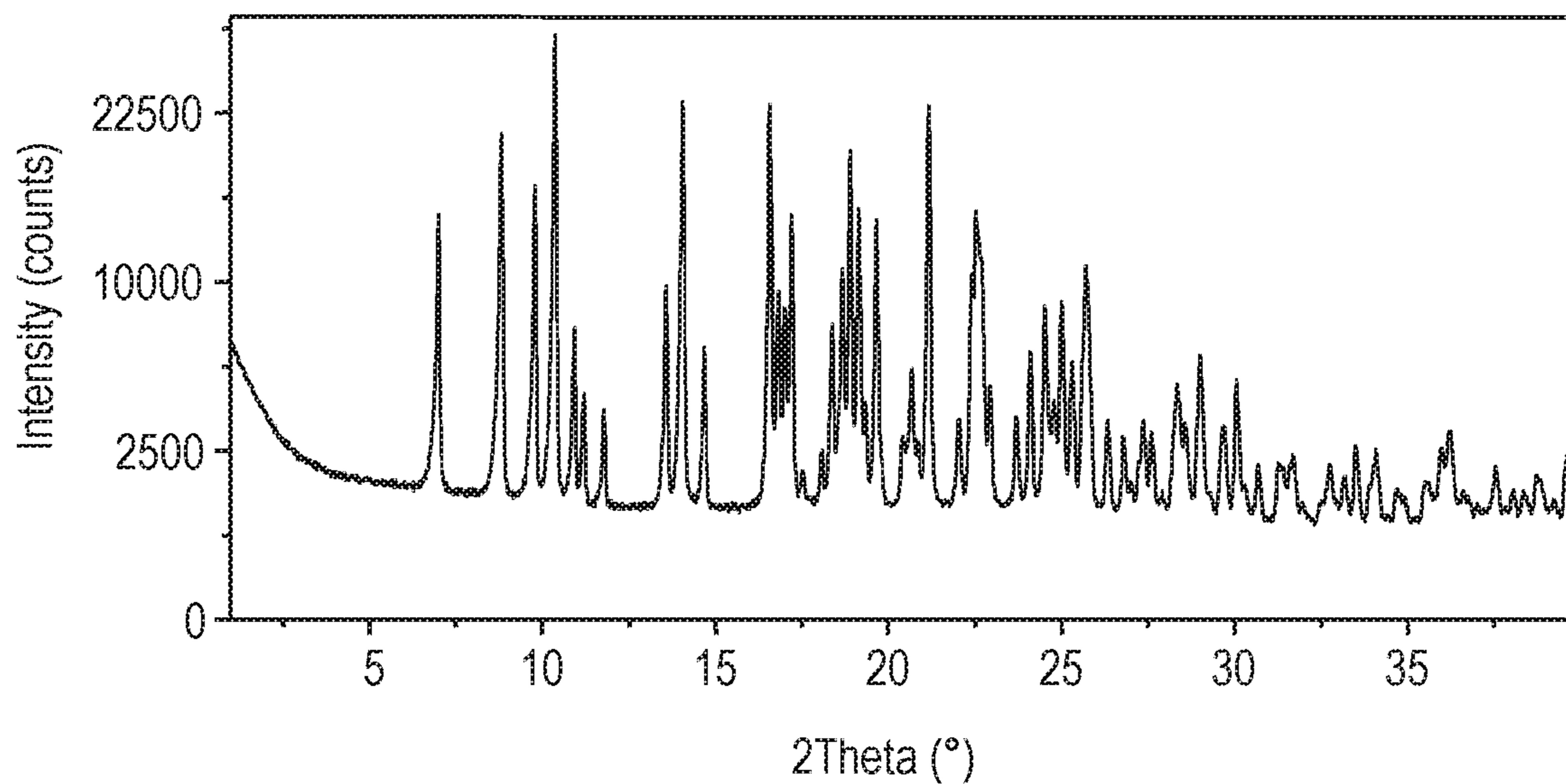


FIG. 29

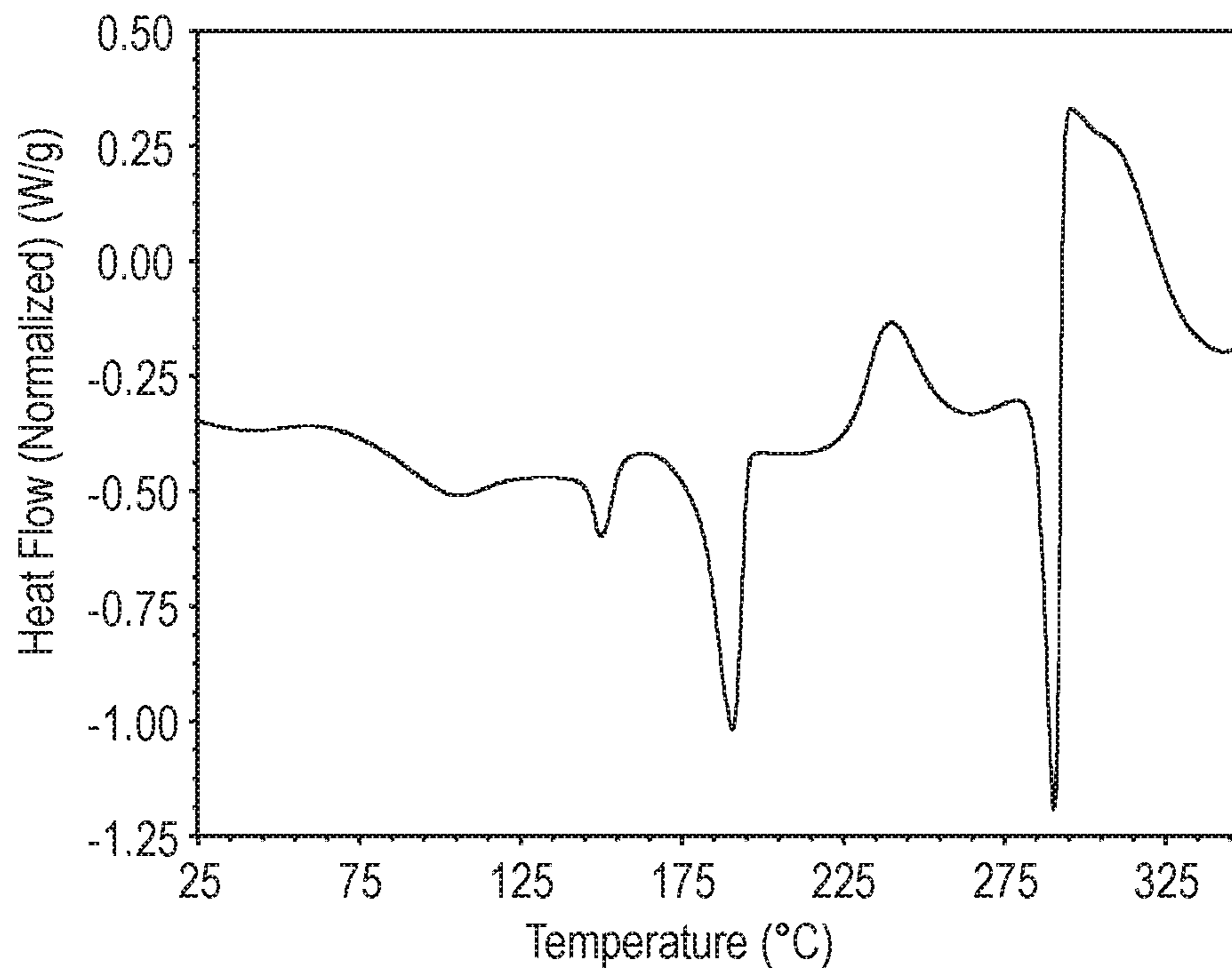


FIG. 30

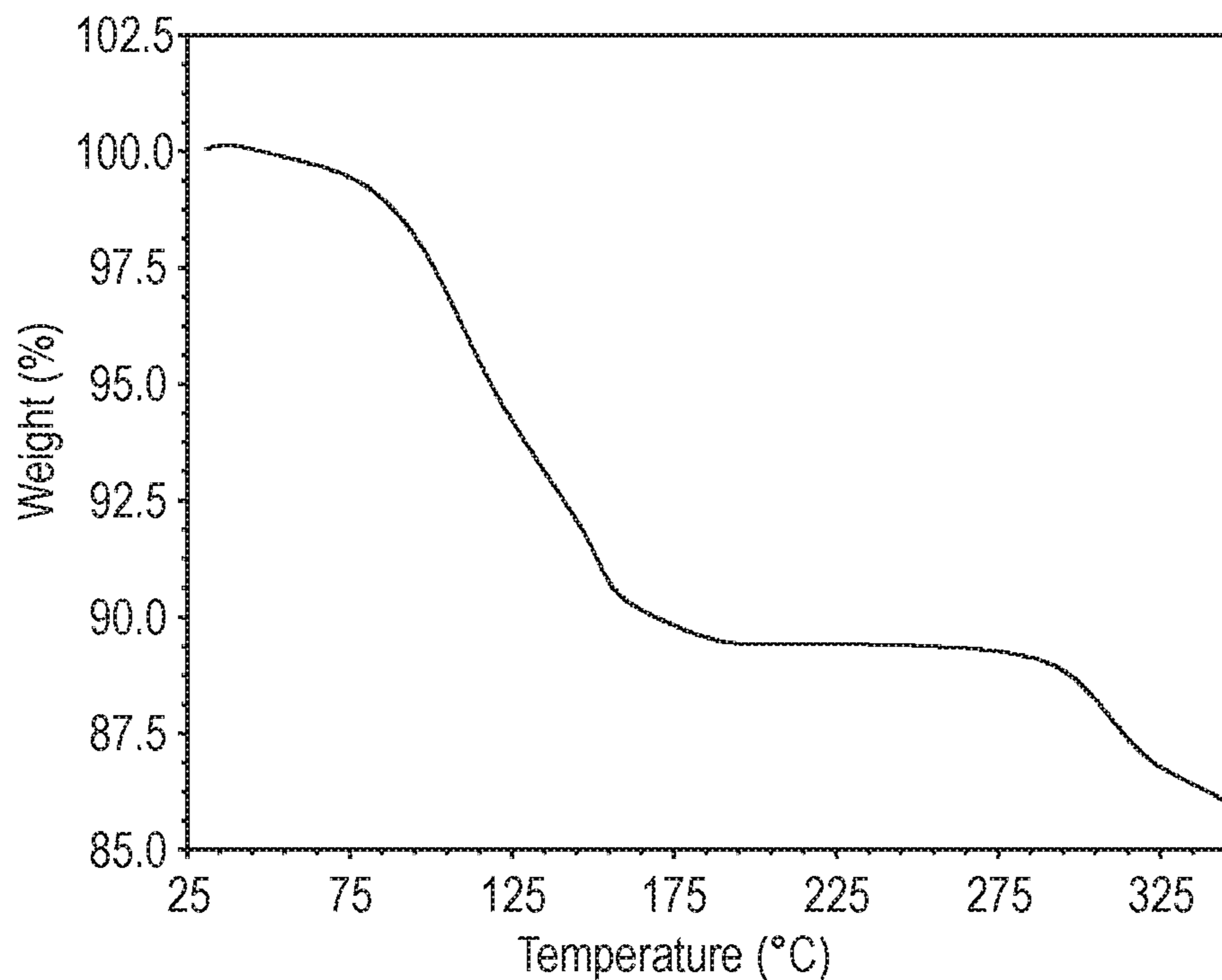


FIG. 31

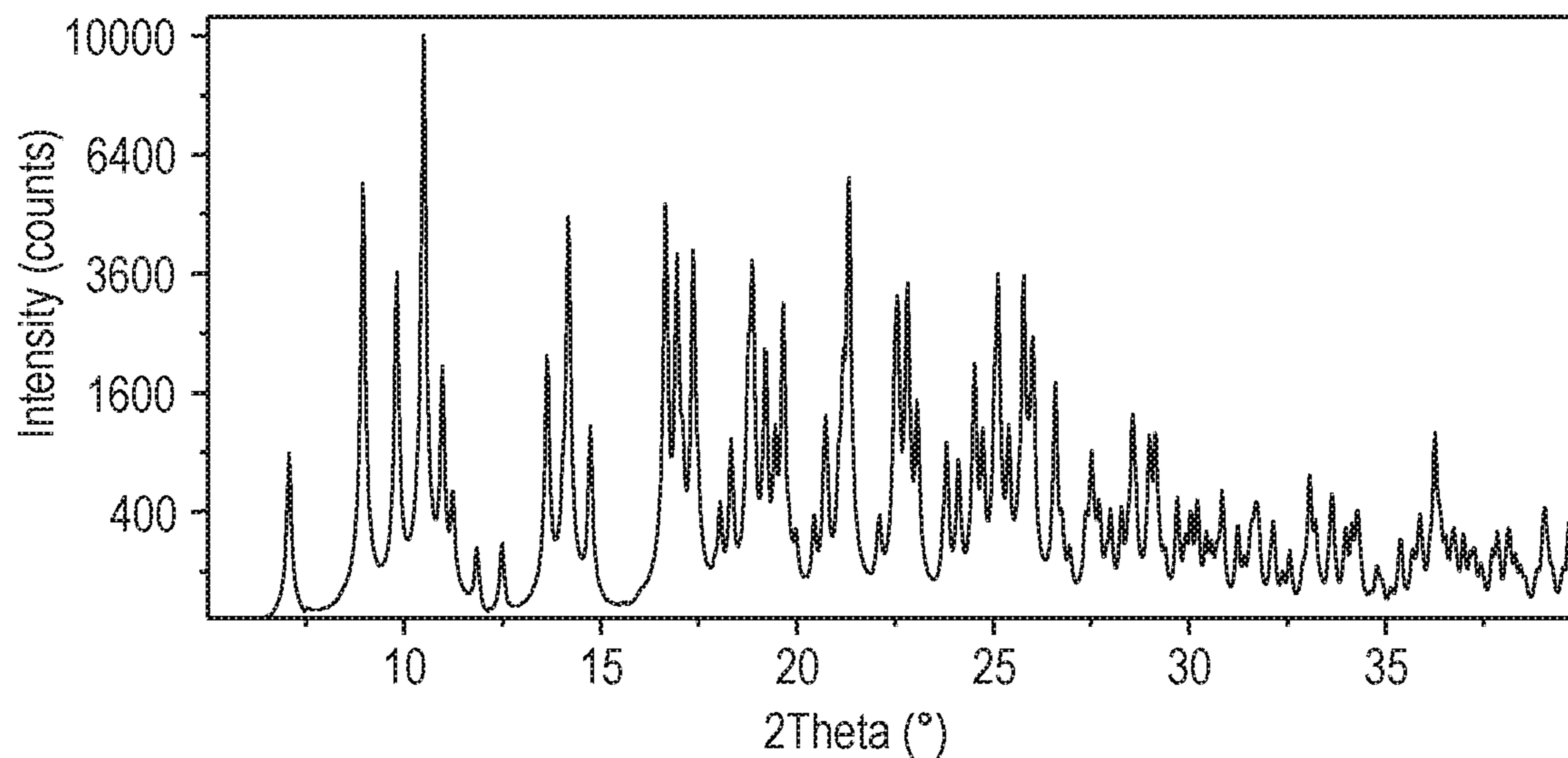


FIG. 32

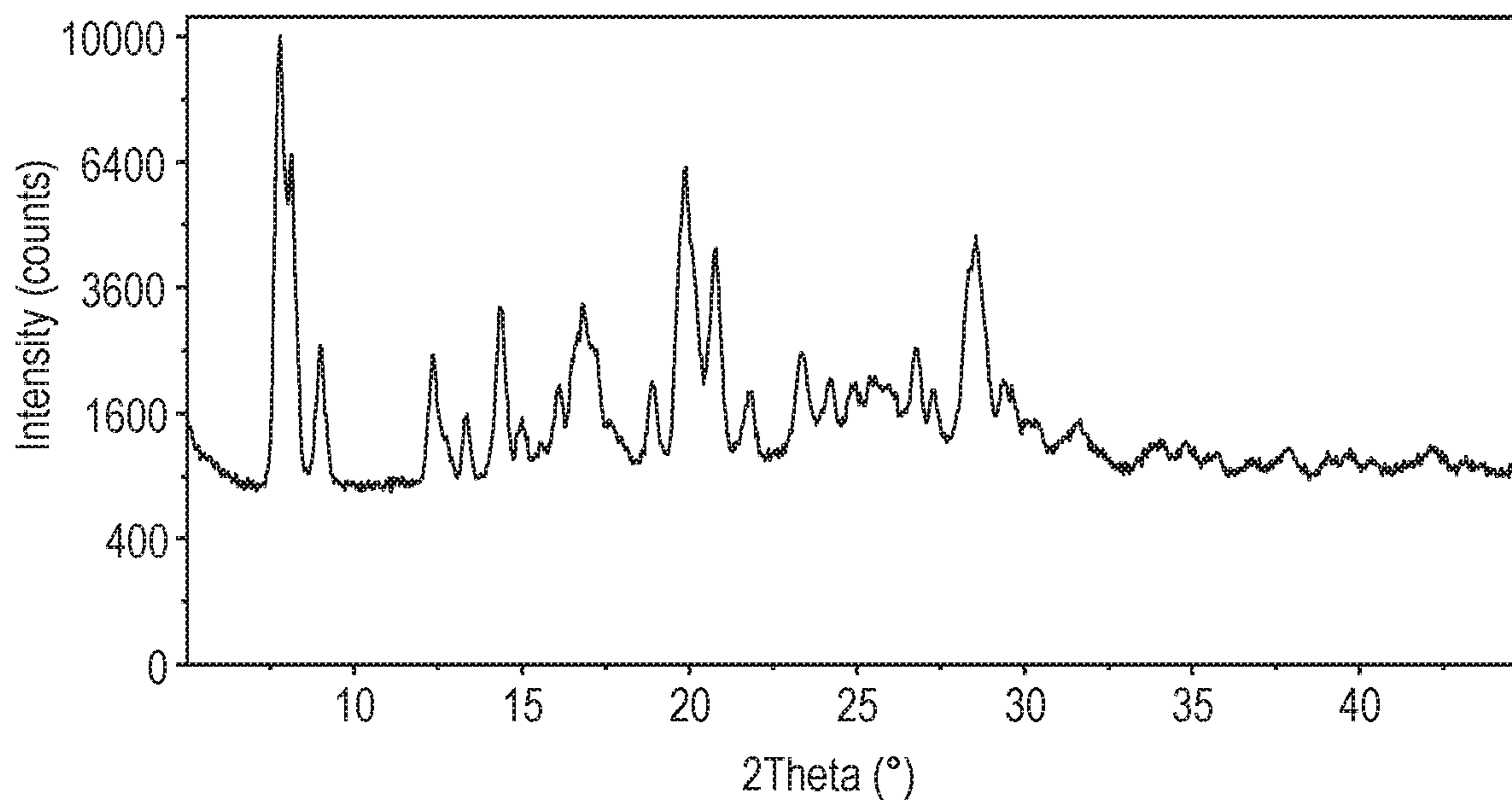


FIG. 33

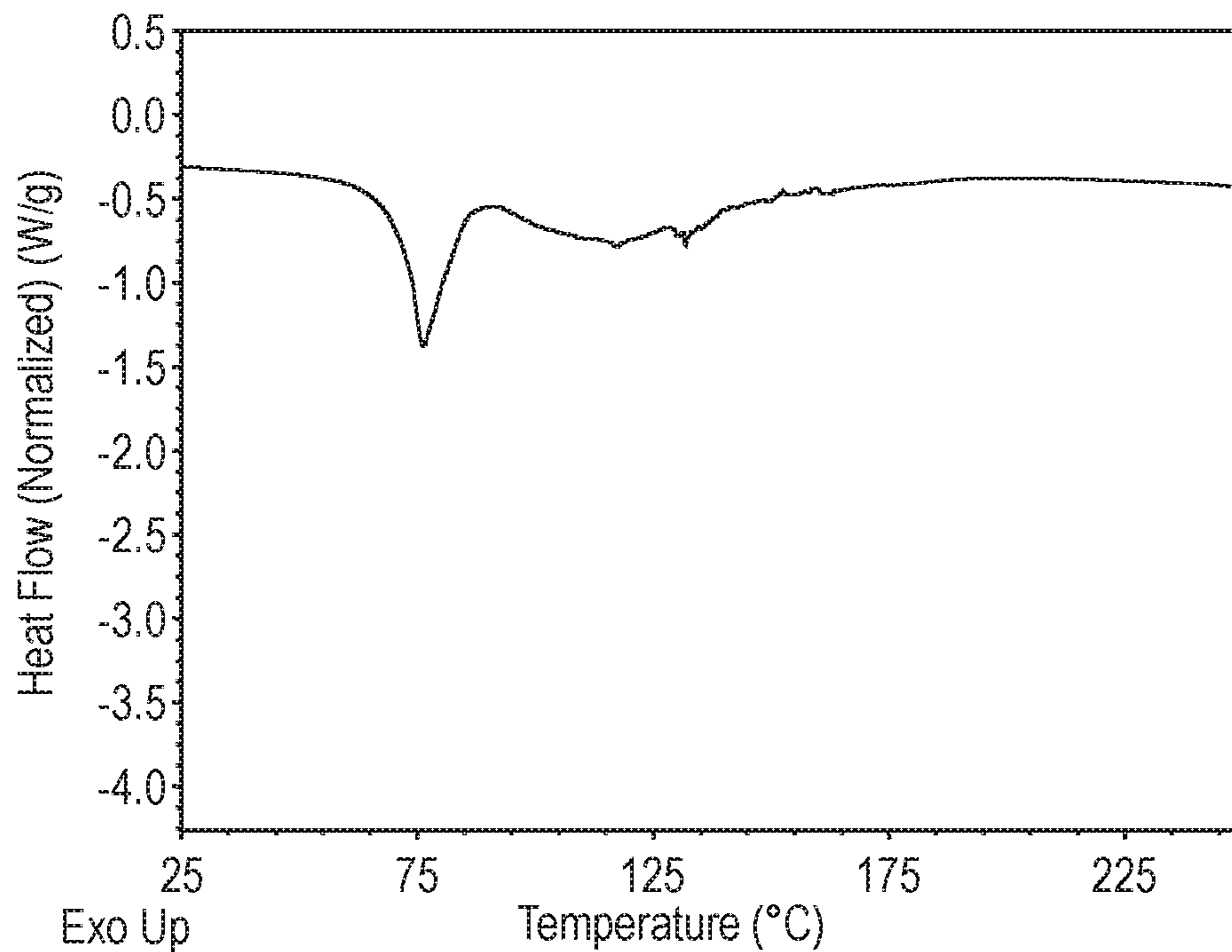


FIG. 34

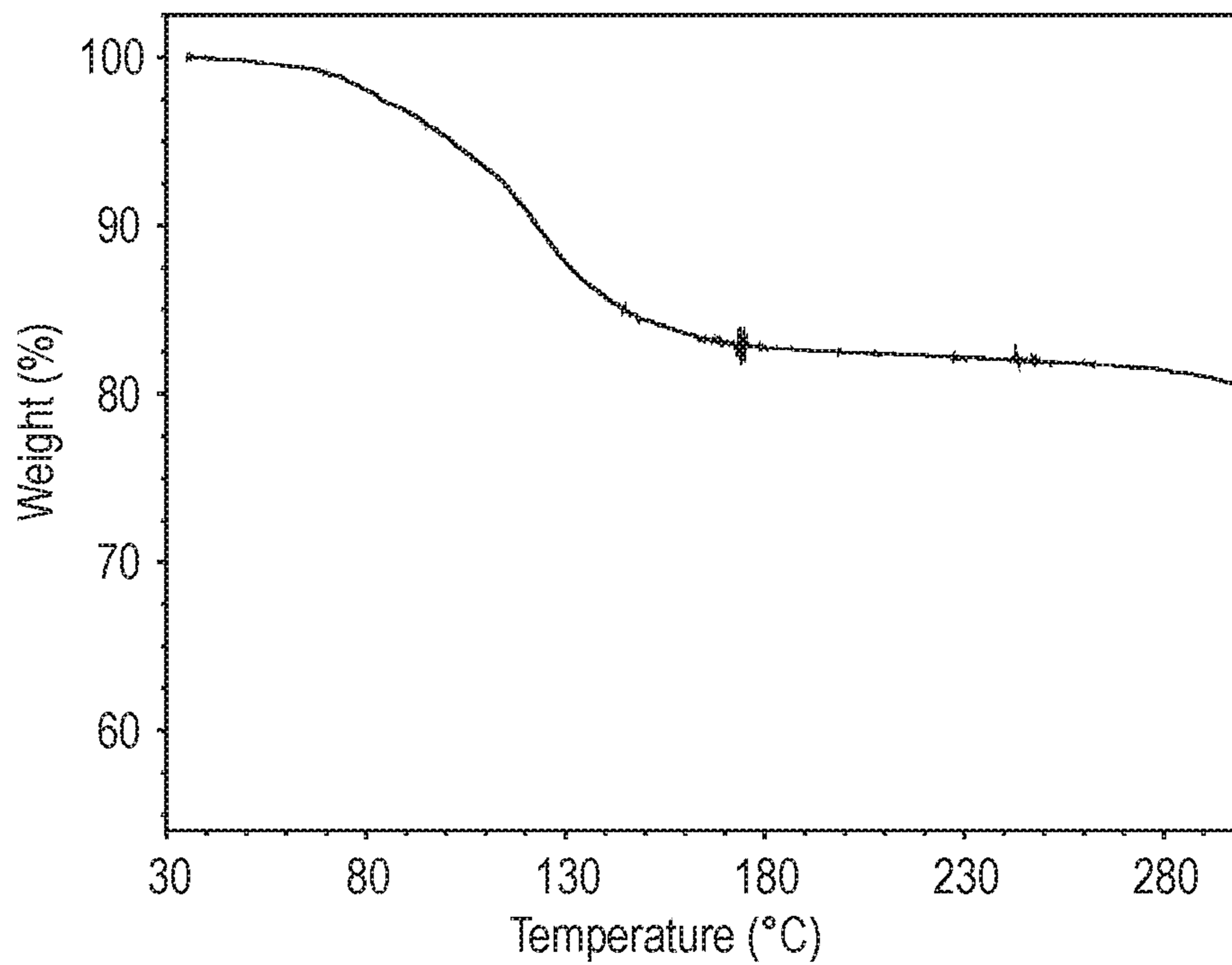


FIG. 35

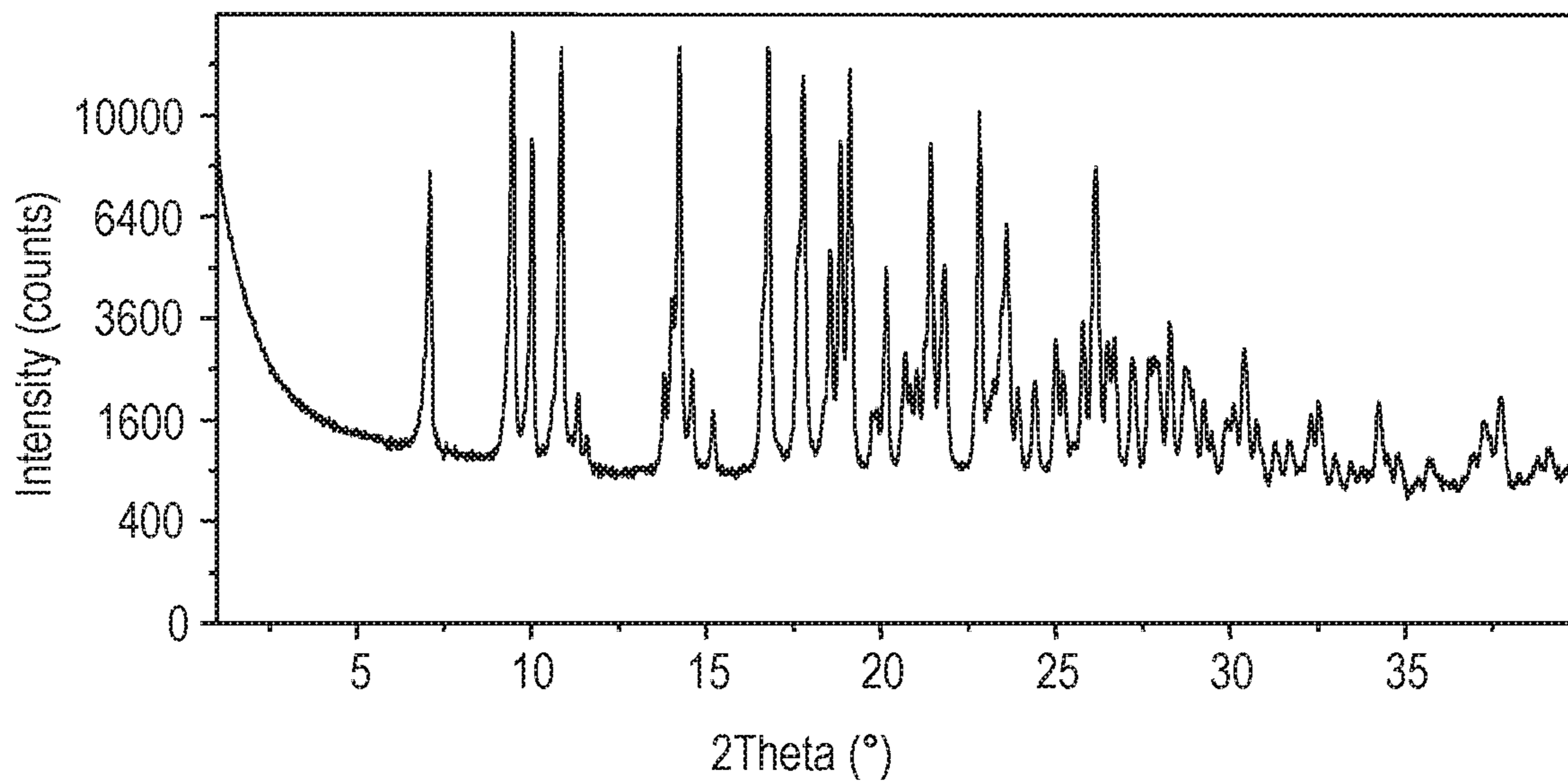


FIG. 36

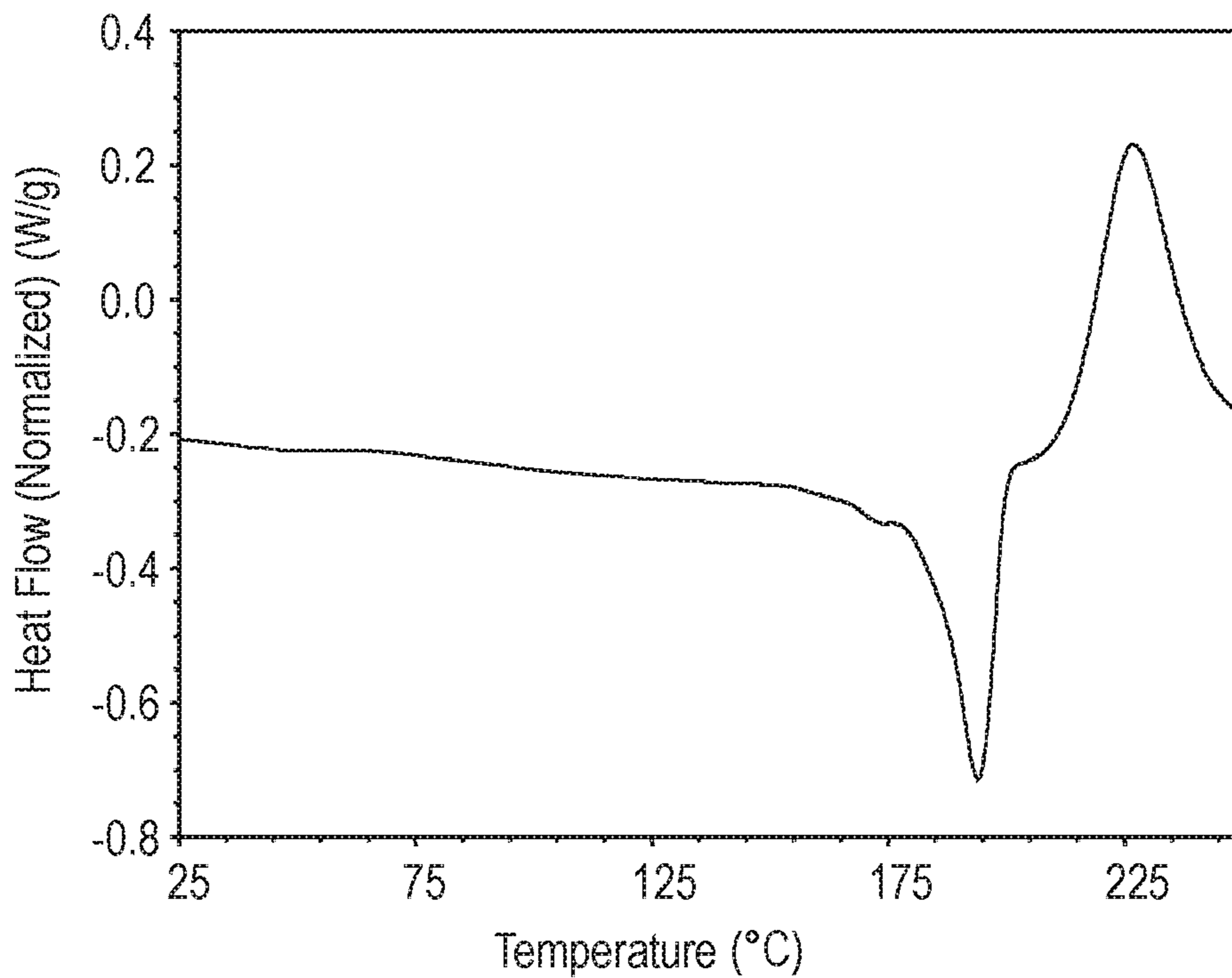


FIG. 37

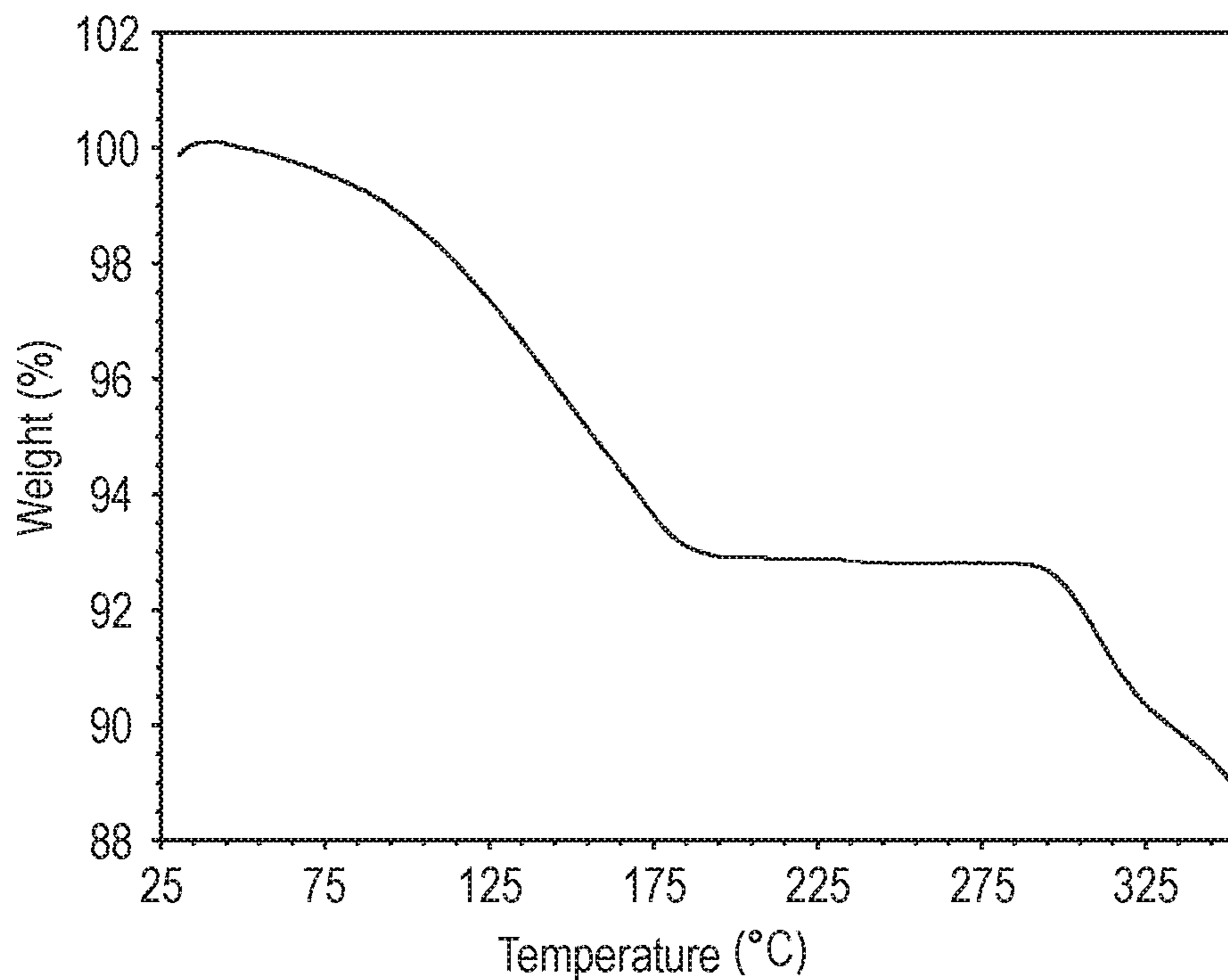


FIG. 38

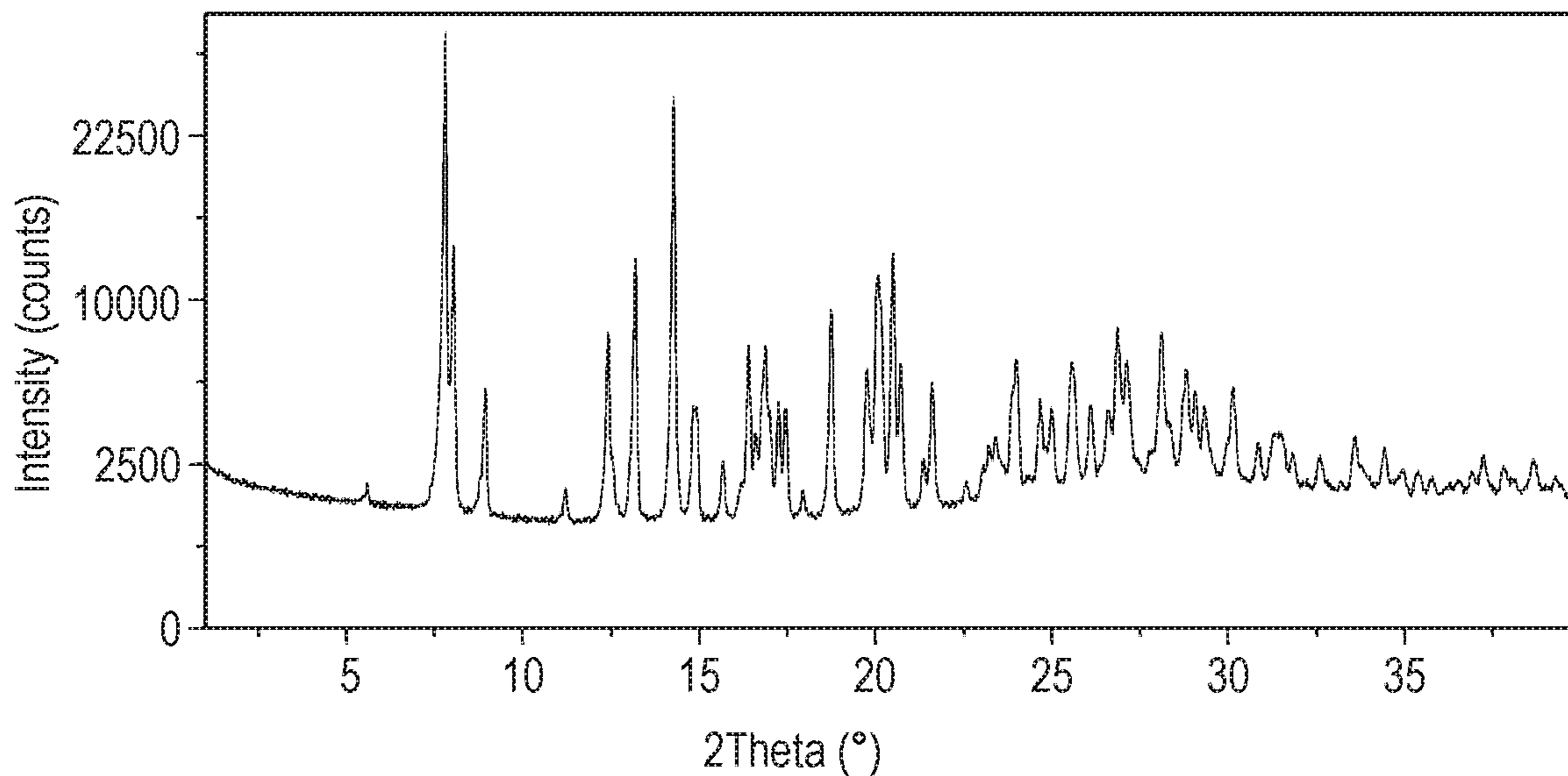


FIG. 39

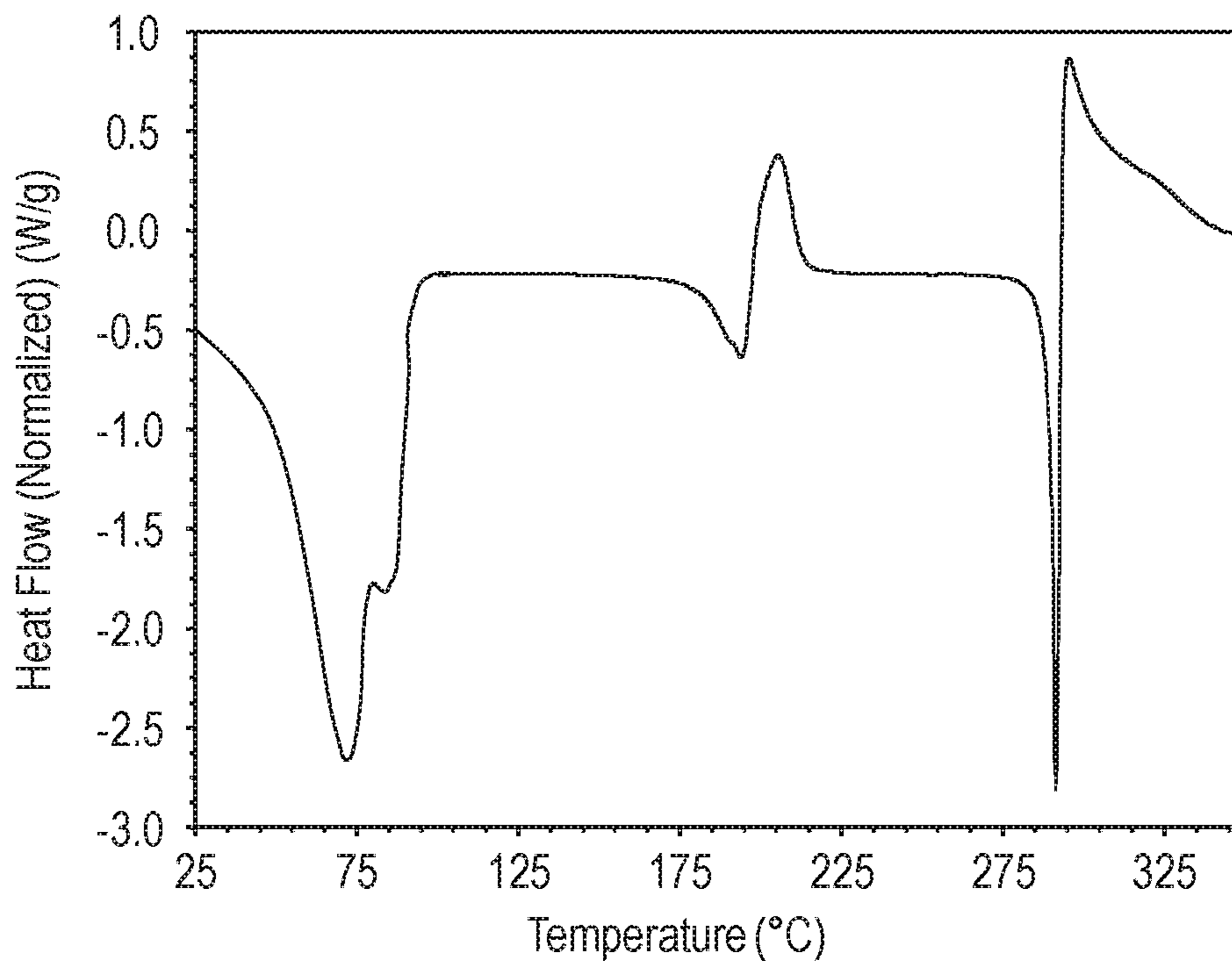


FIG. 40

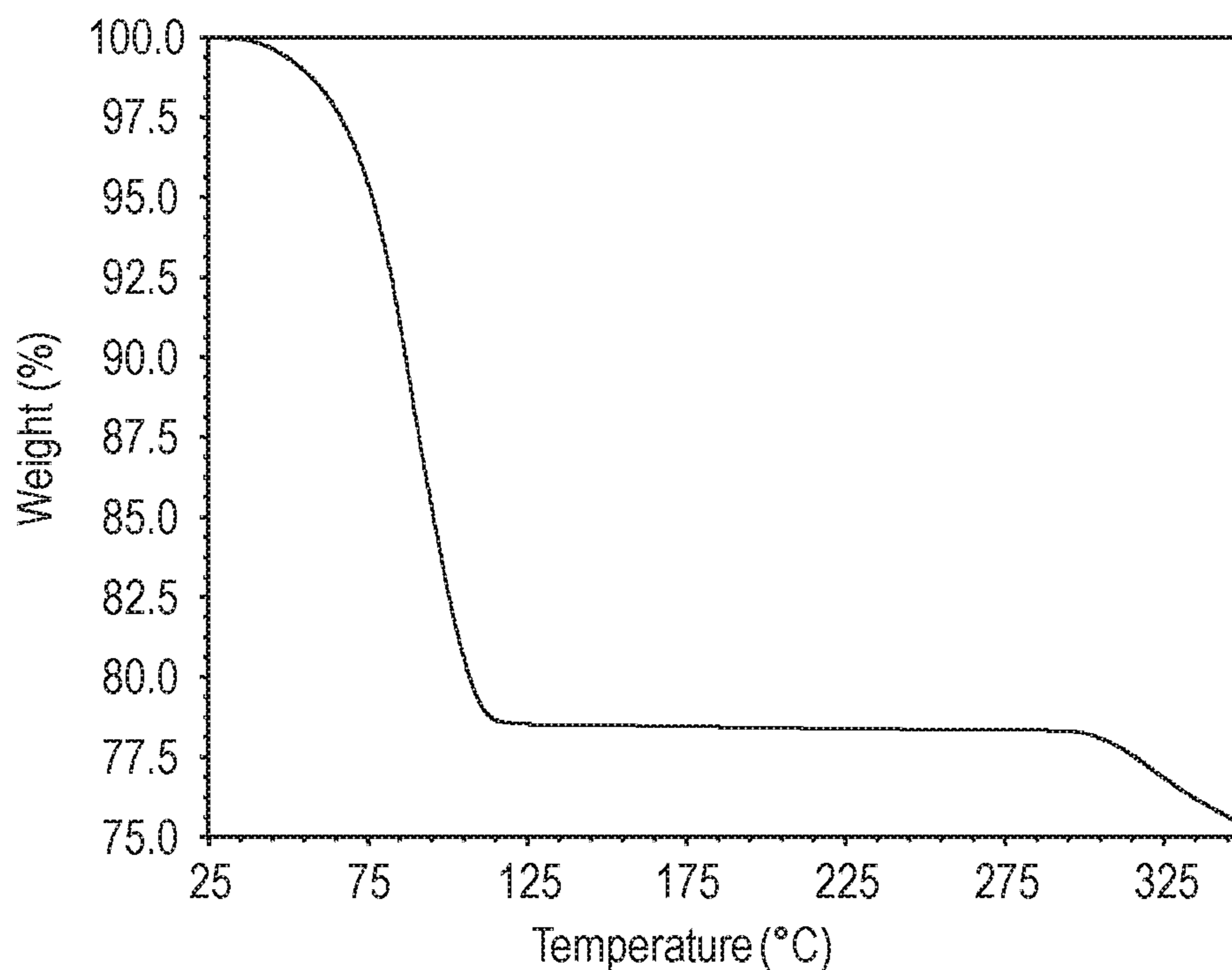


FIG. 41

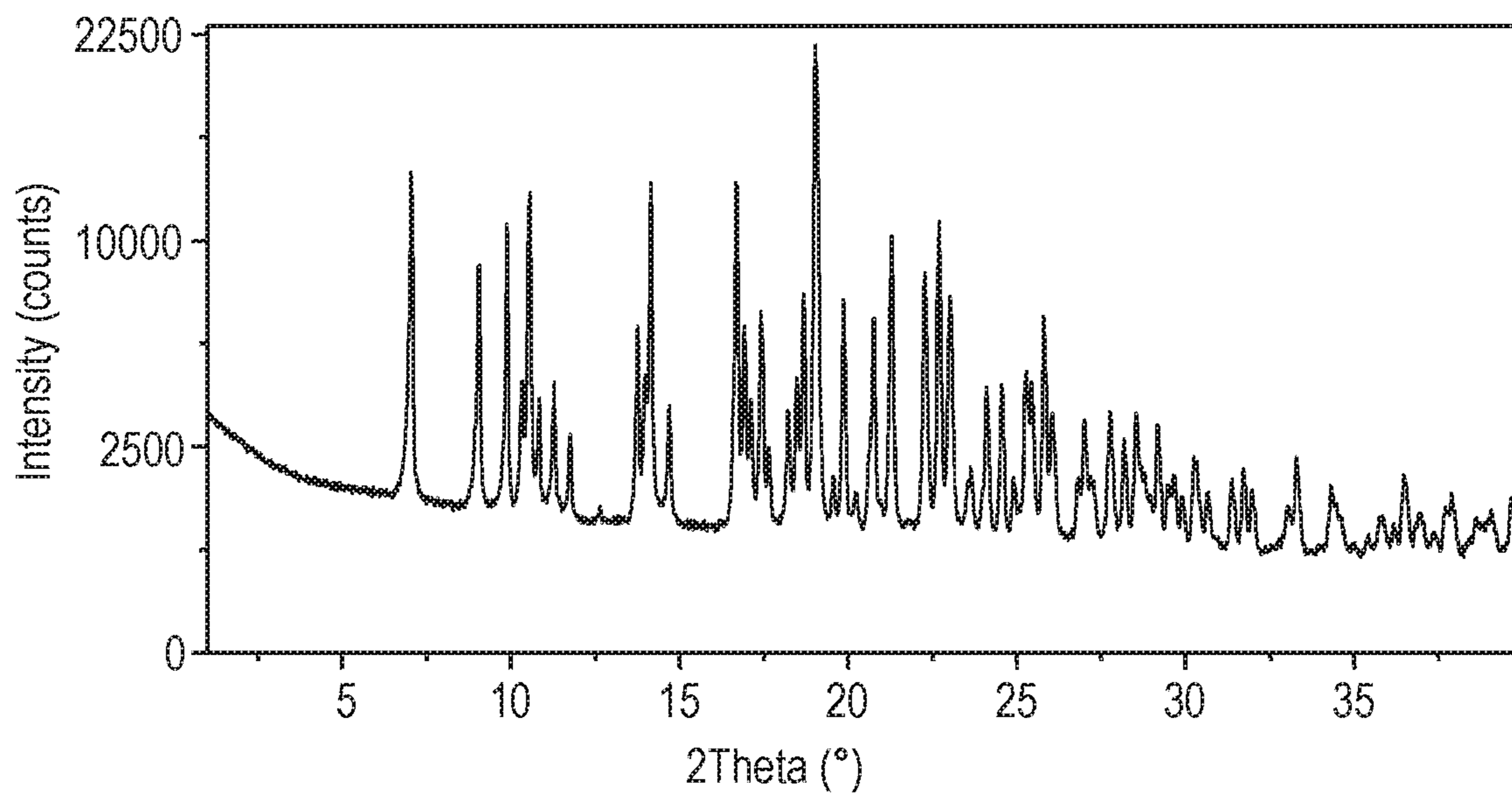


FIG. 42

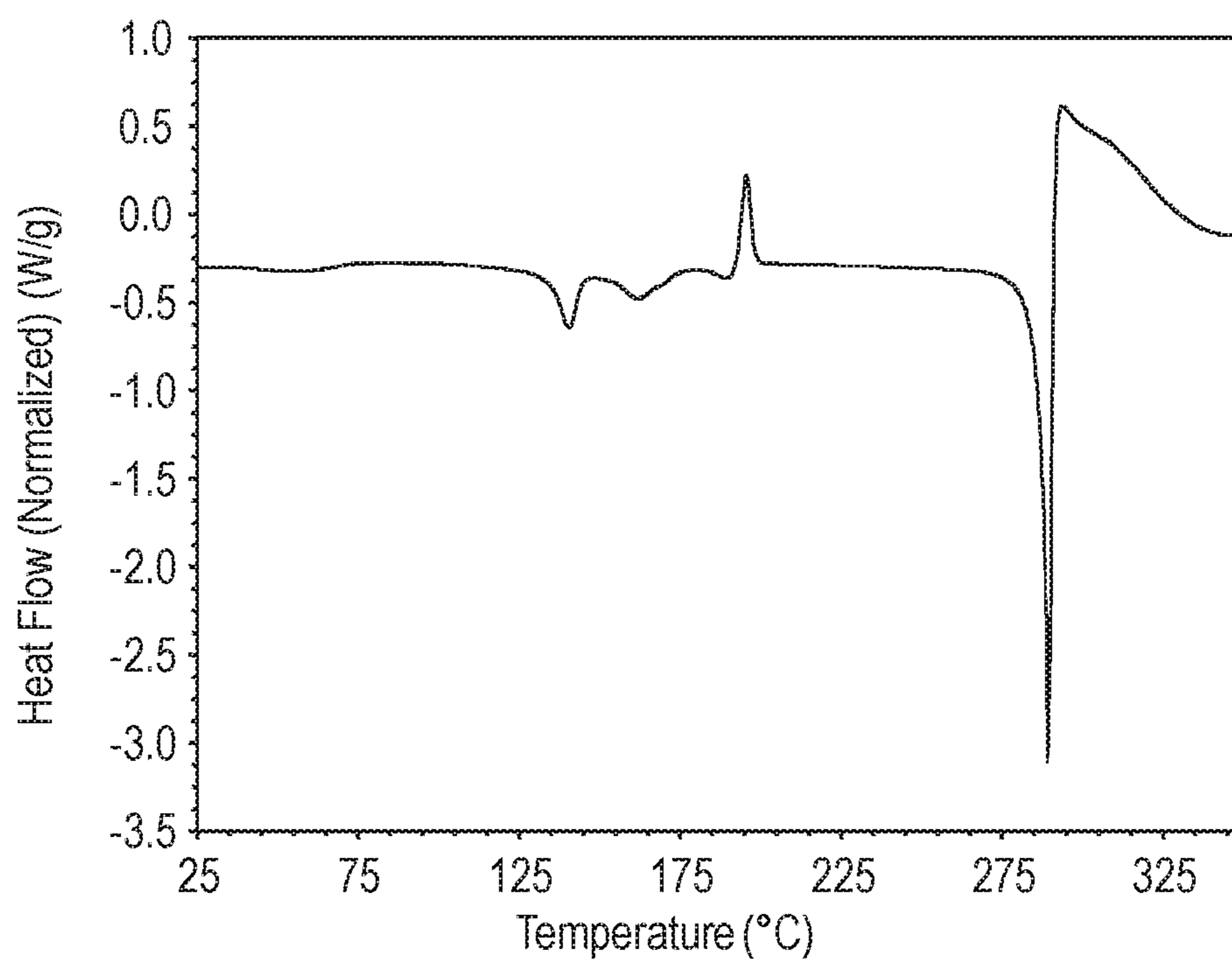


FIG. 43

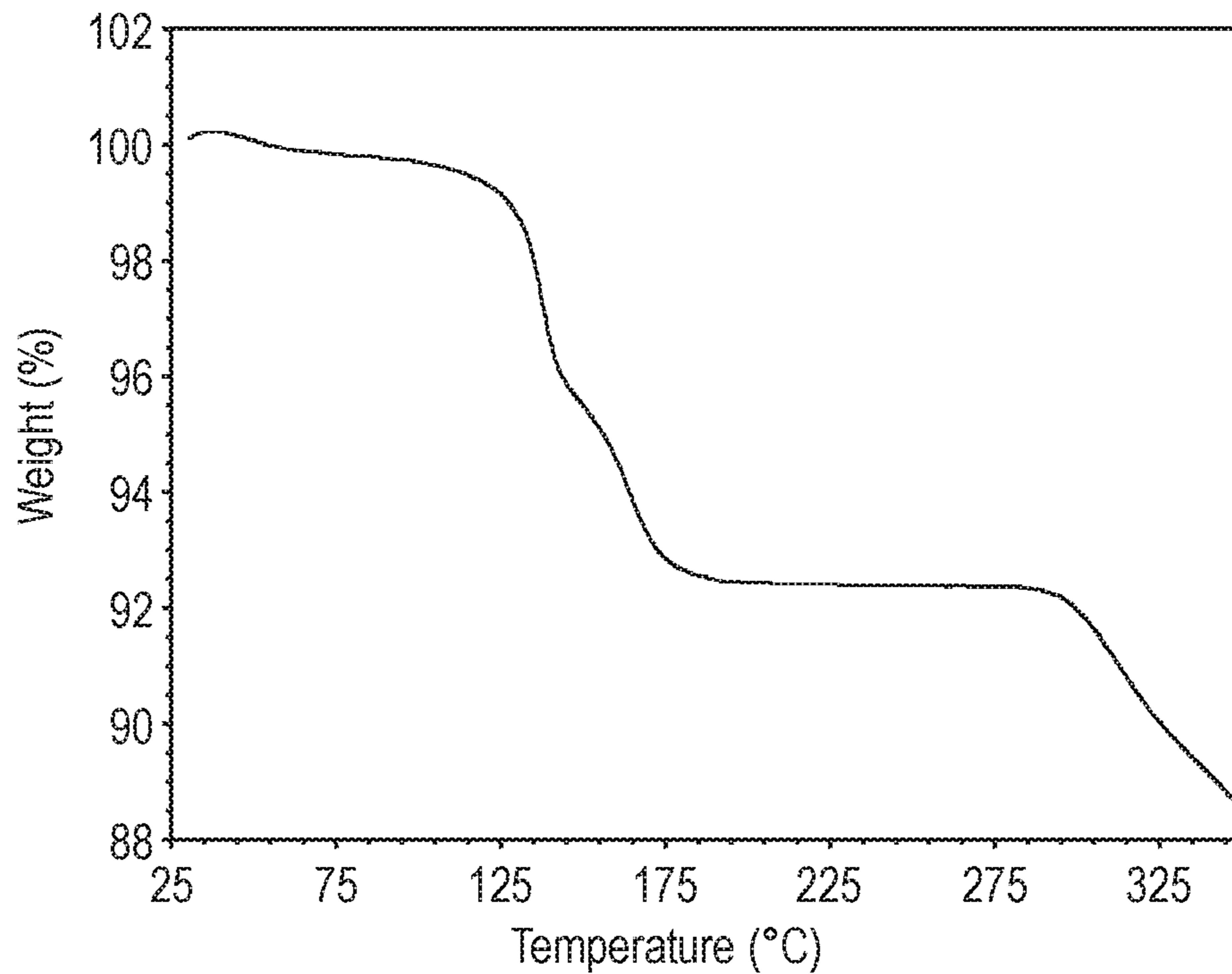


FIG. 44

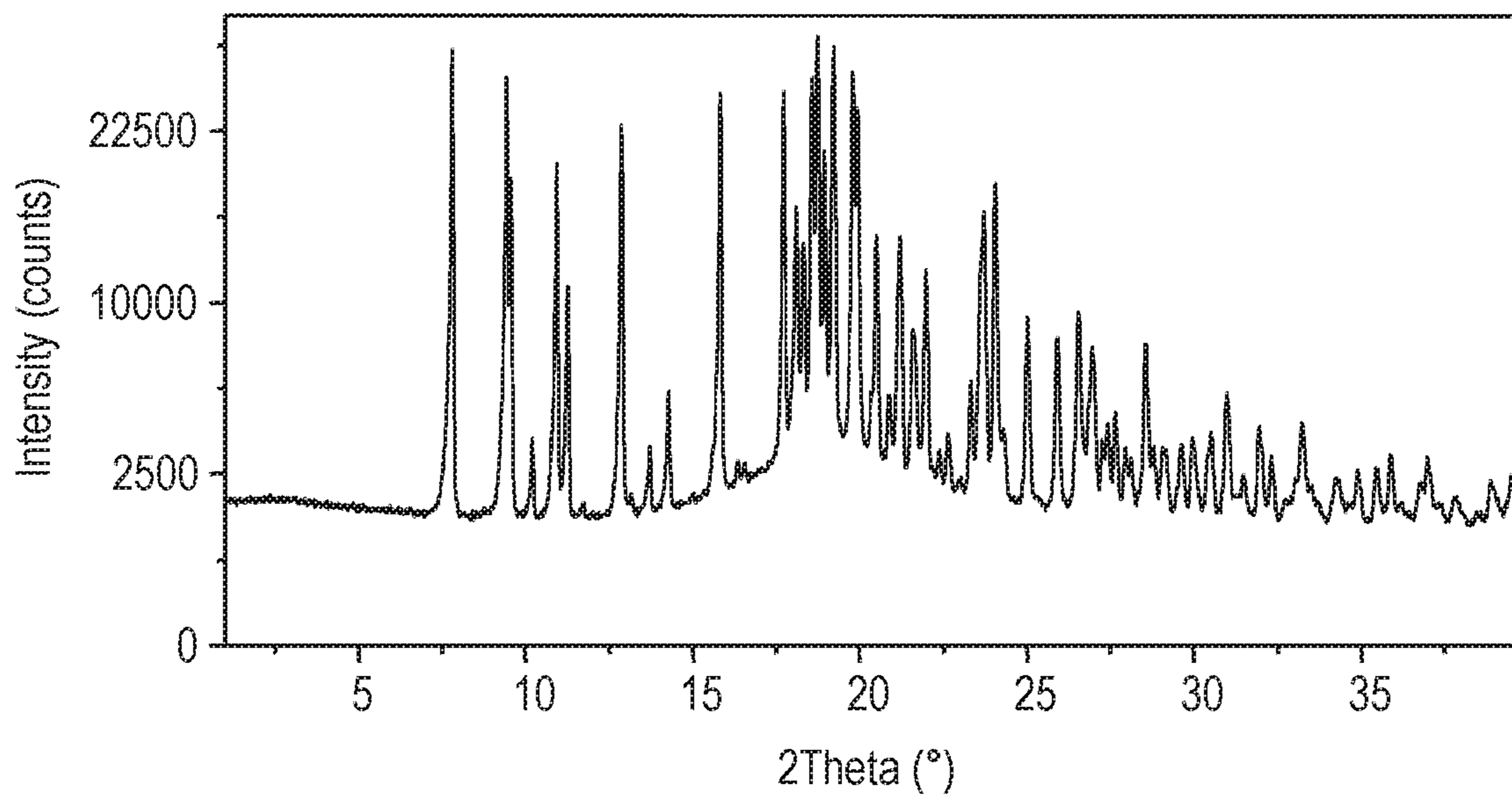


FIG. 45

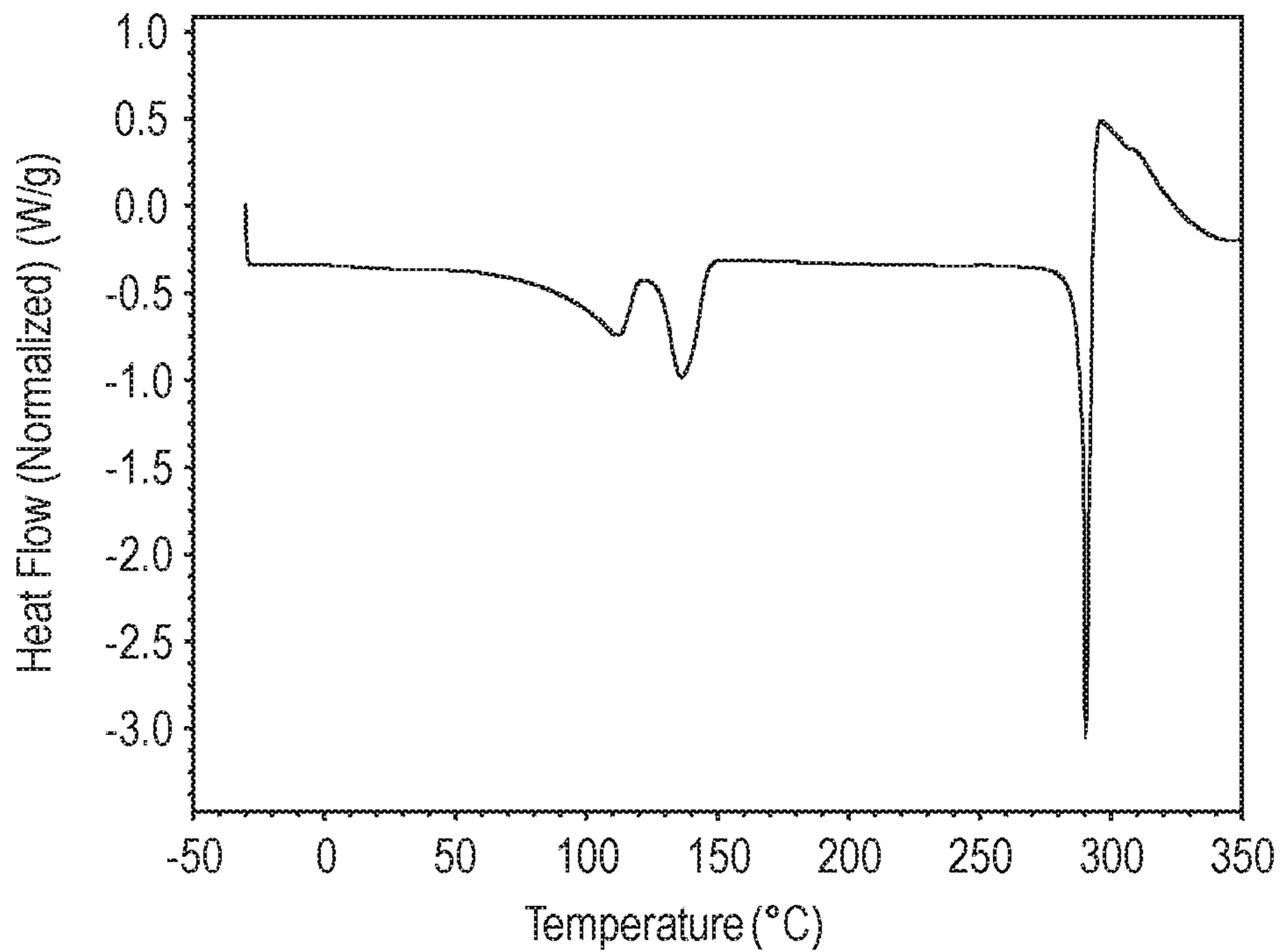


FIG. 46

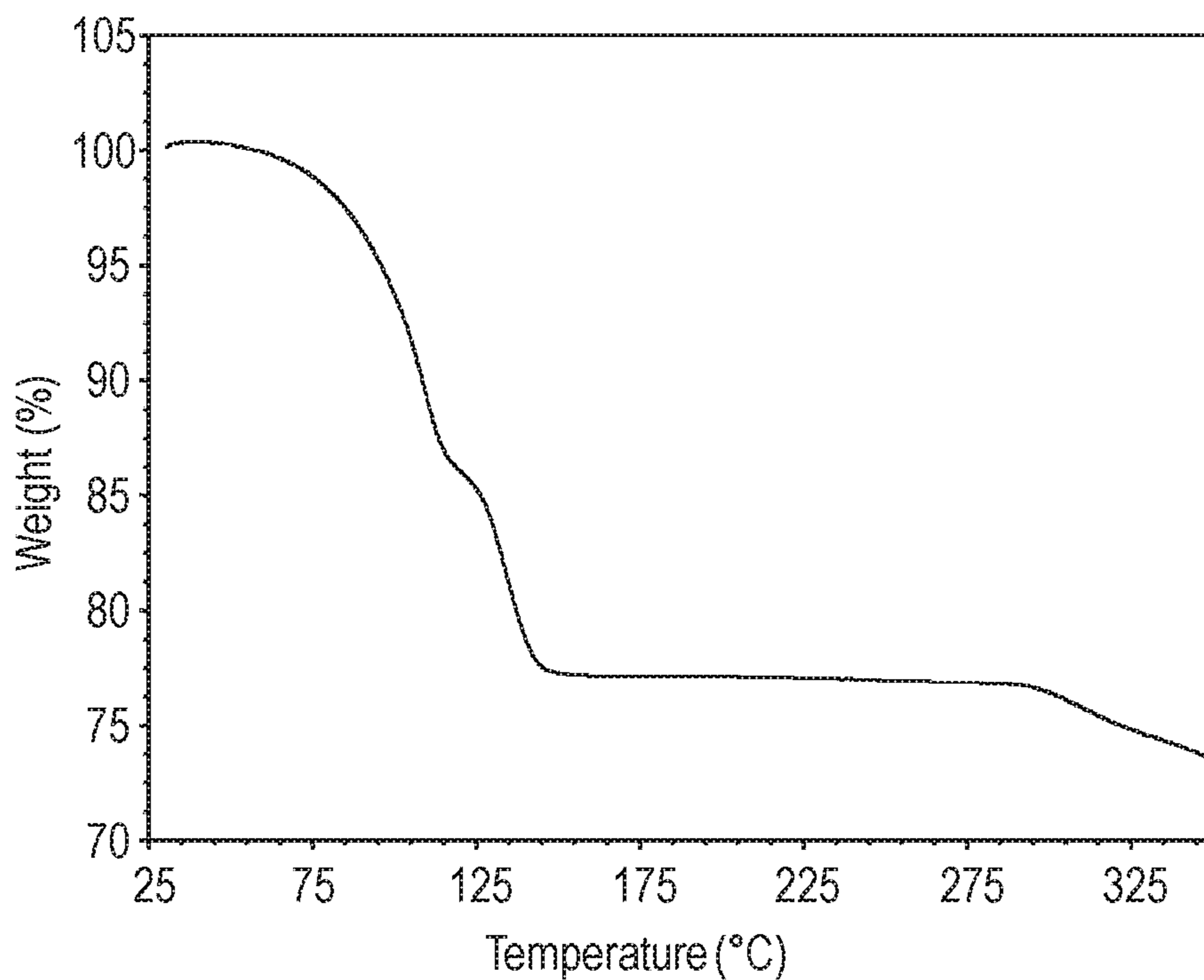


FIG. 47

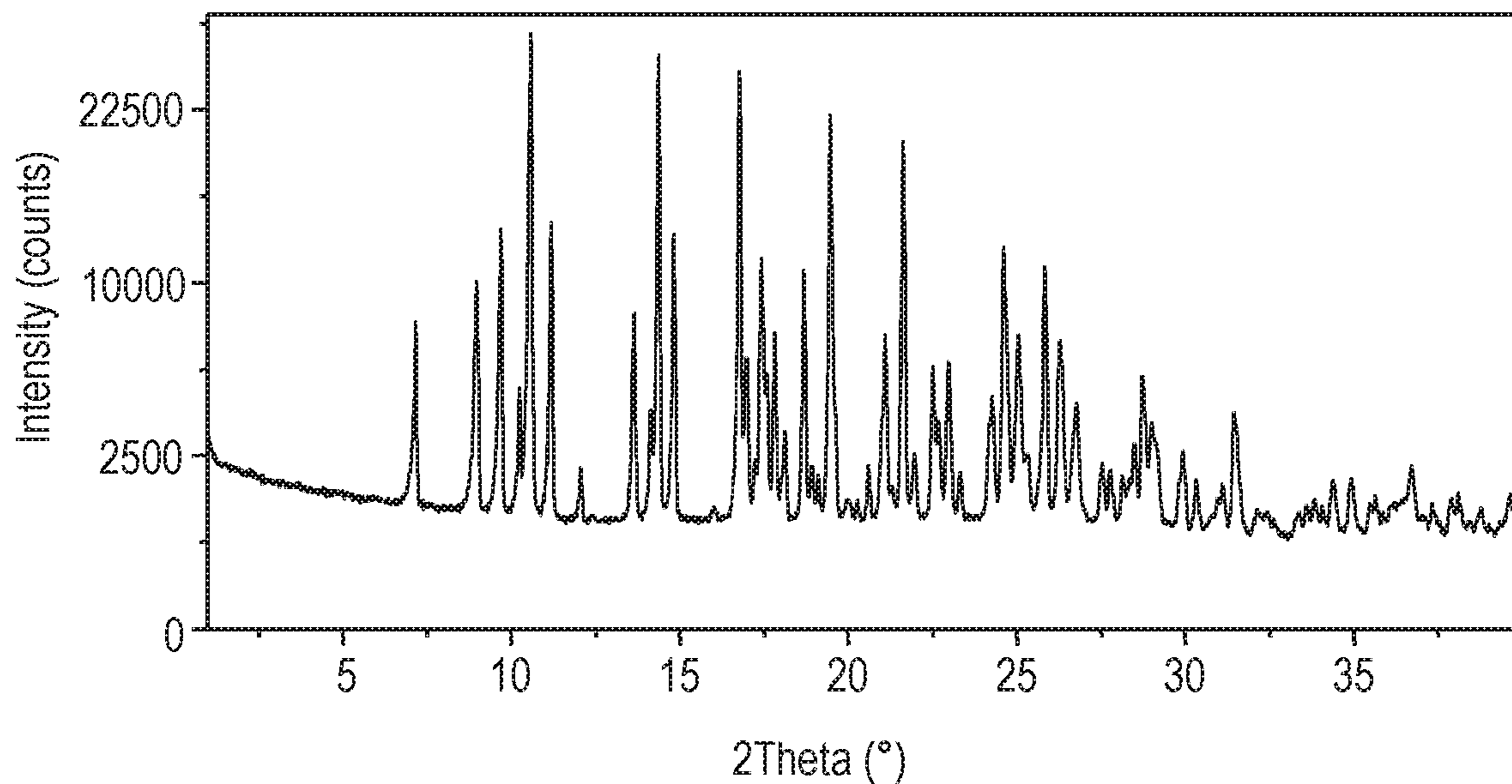


FIG. 48

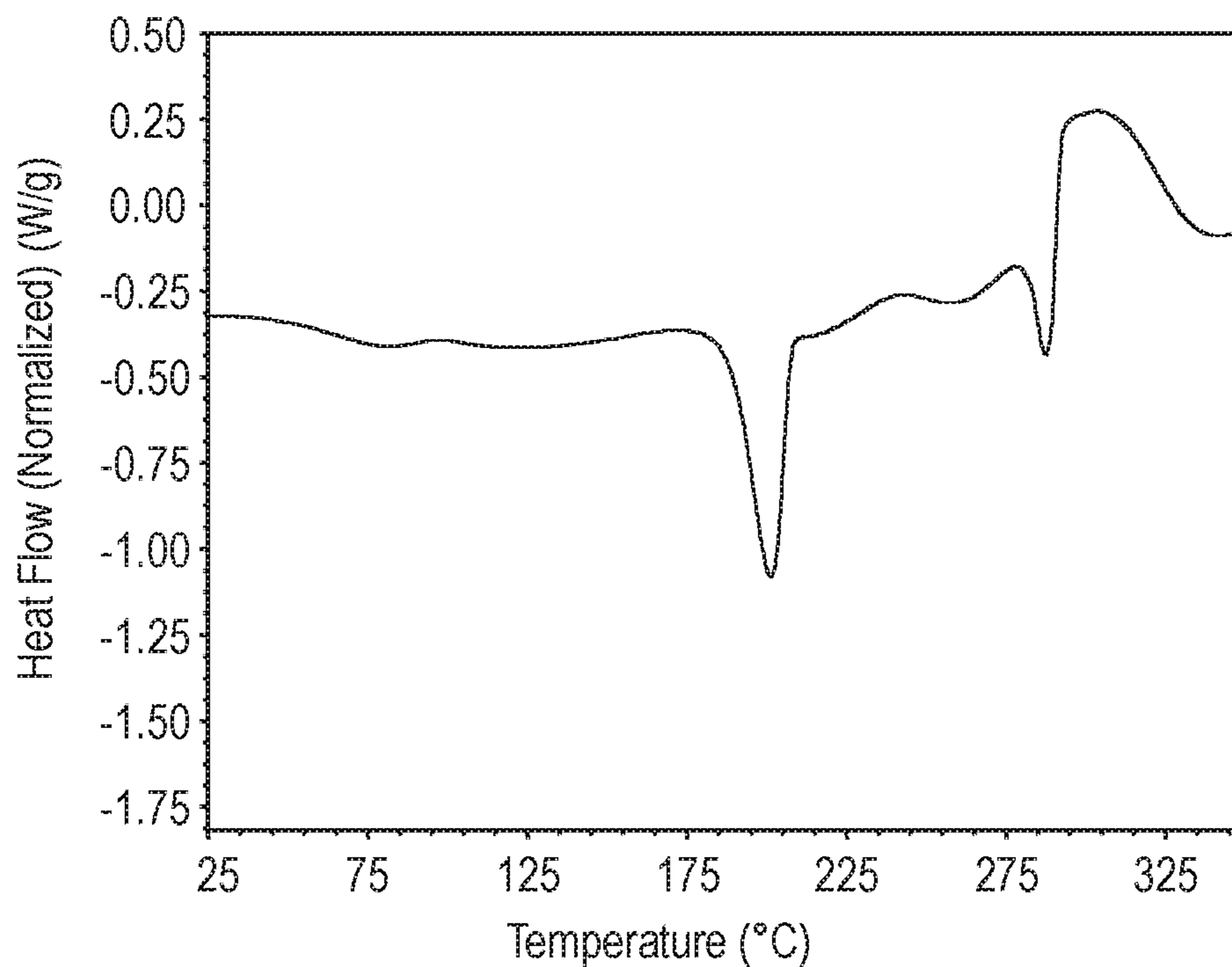


FIG. 49

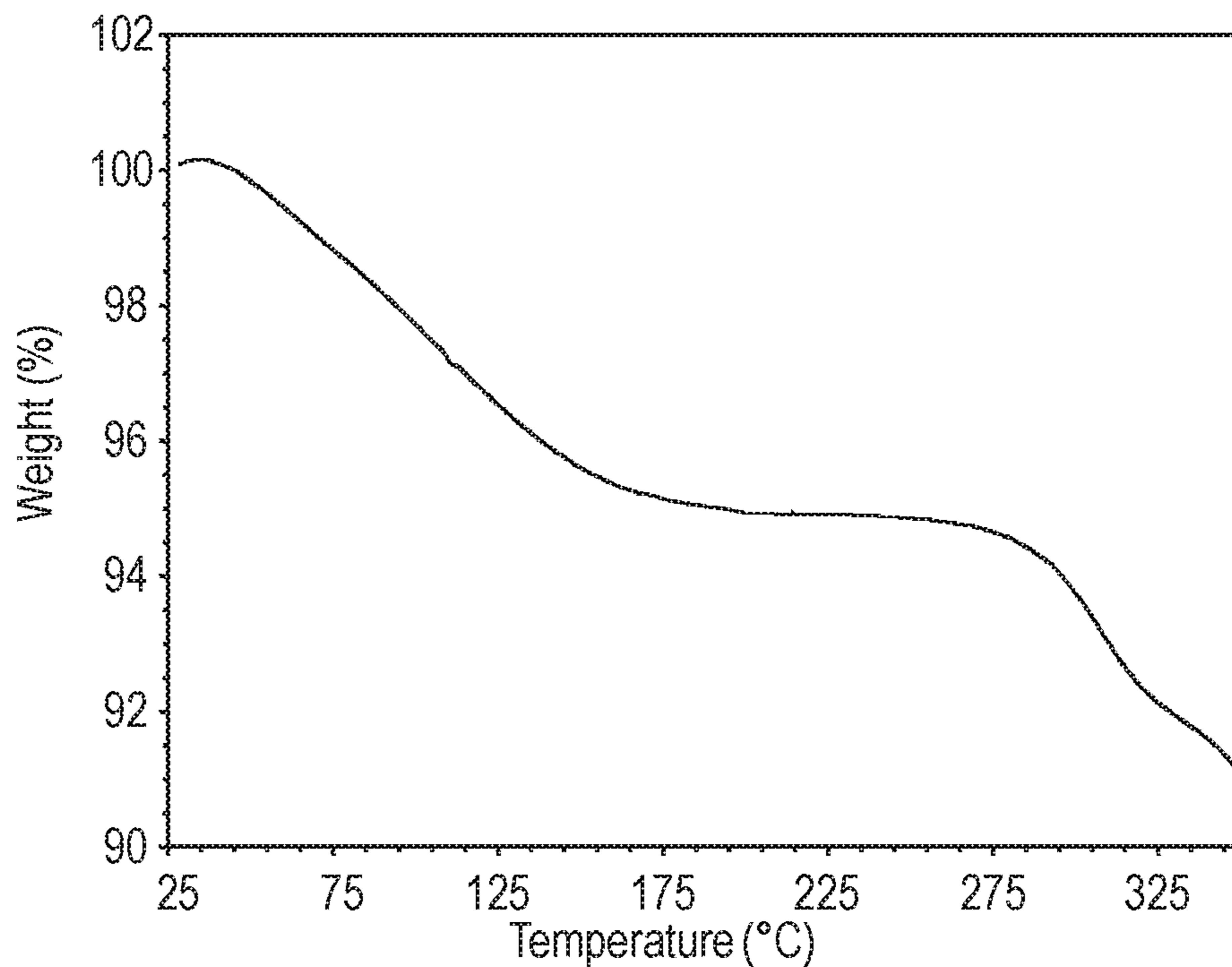


FIG. 50

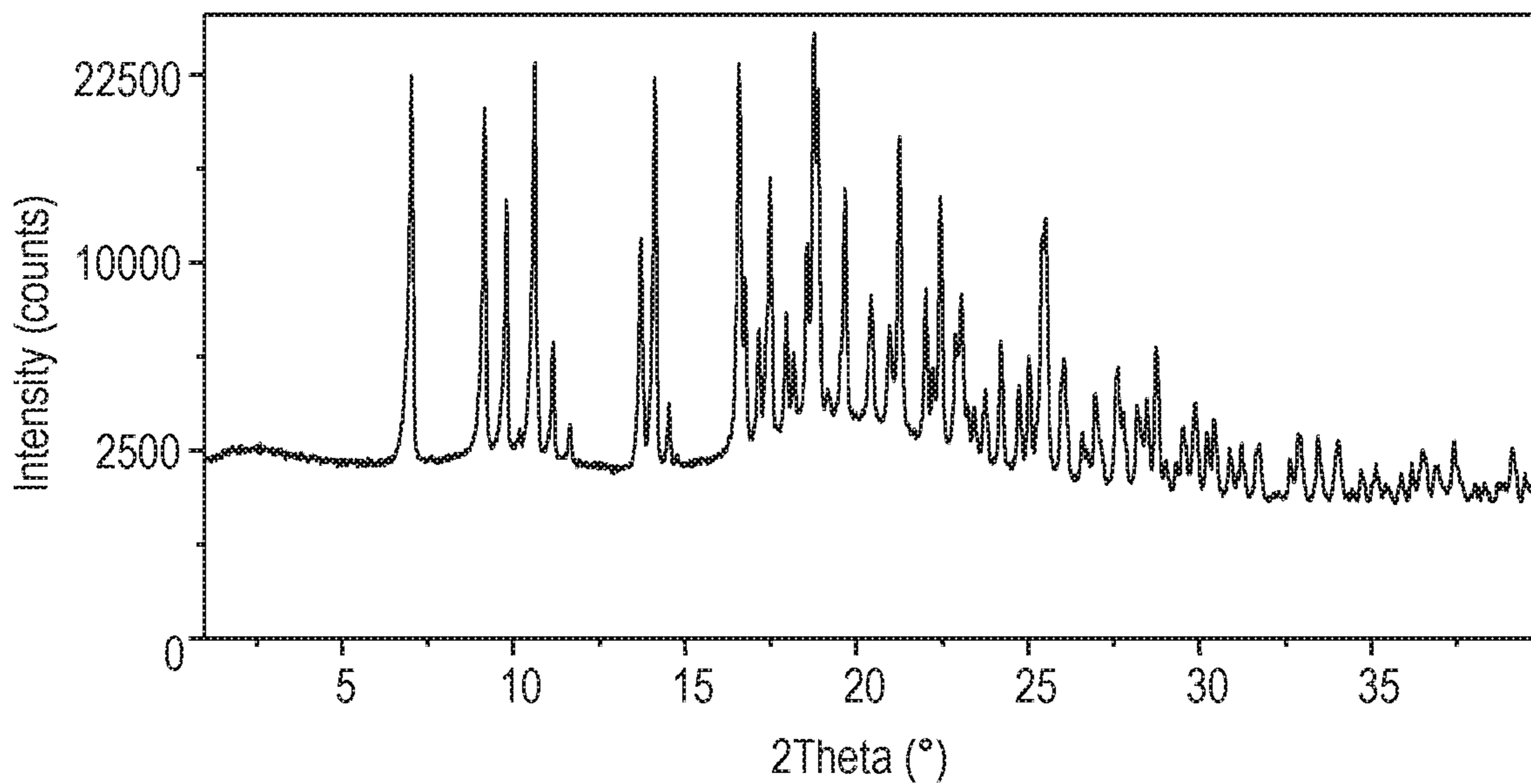


FIG. 51

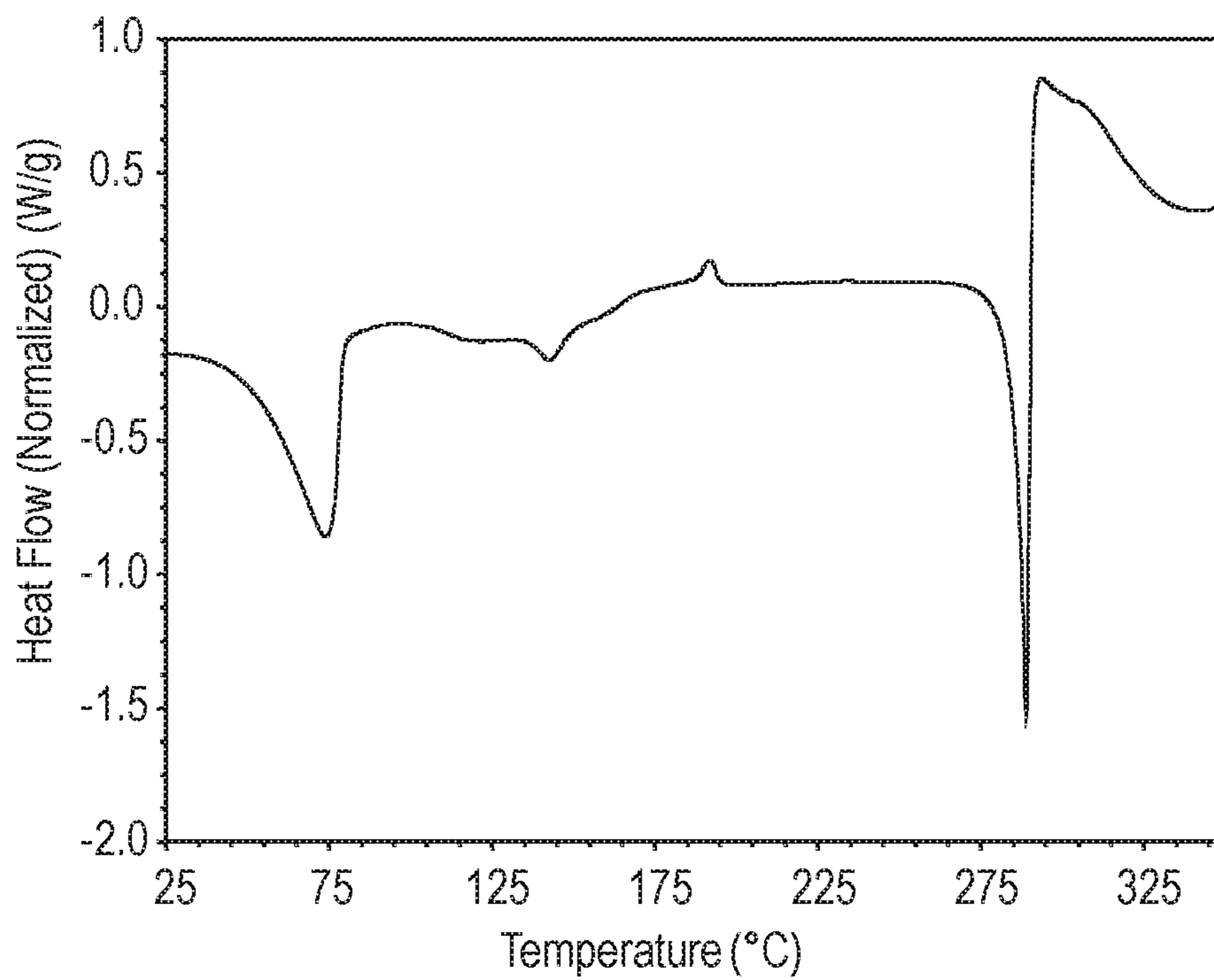


FIG. 52

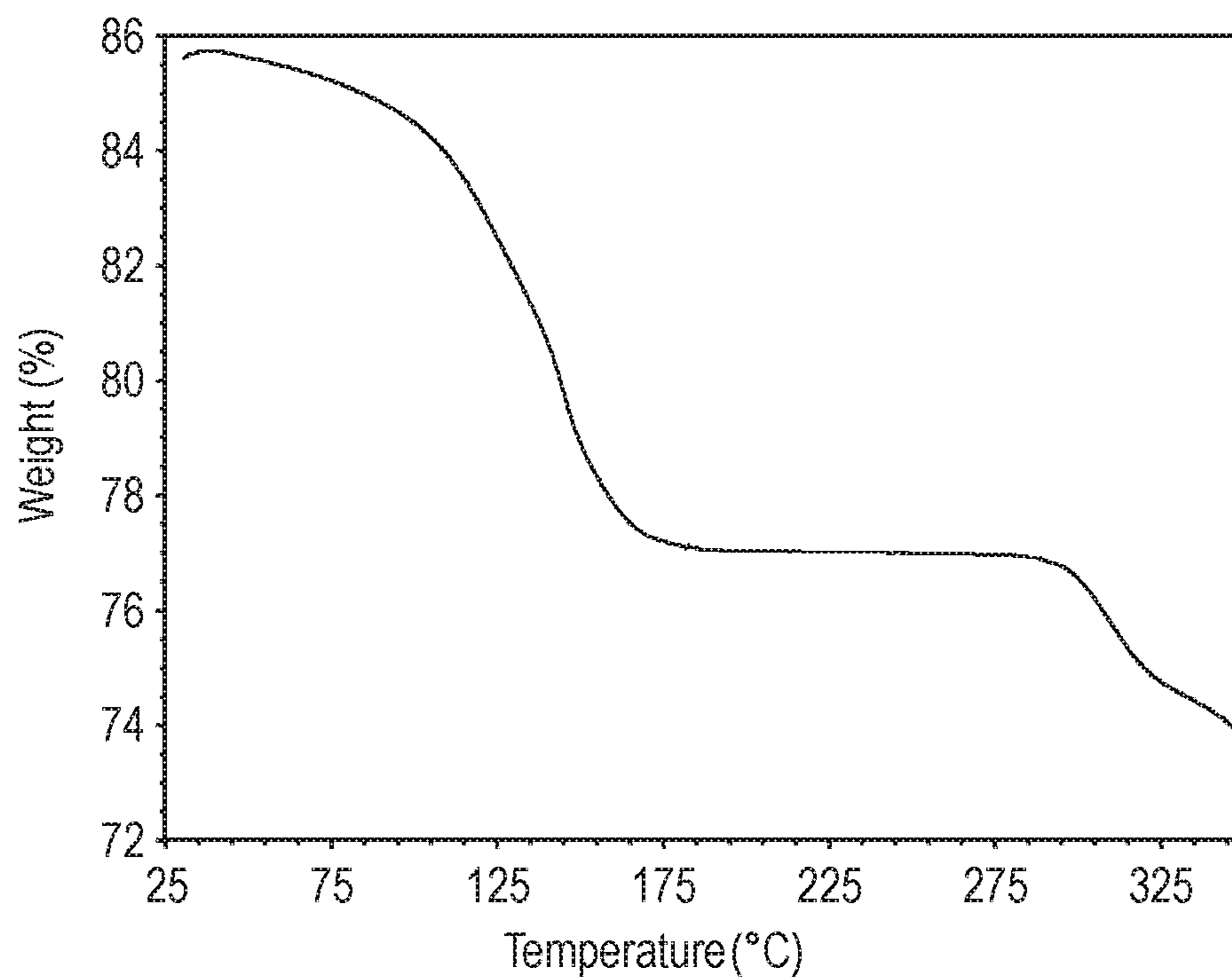


FIG. 53

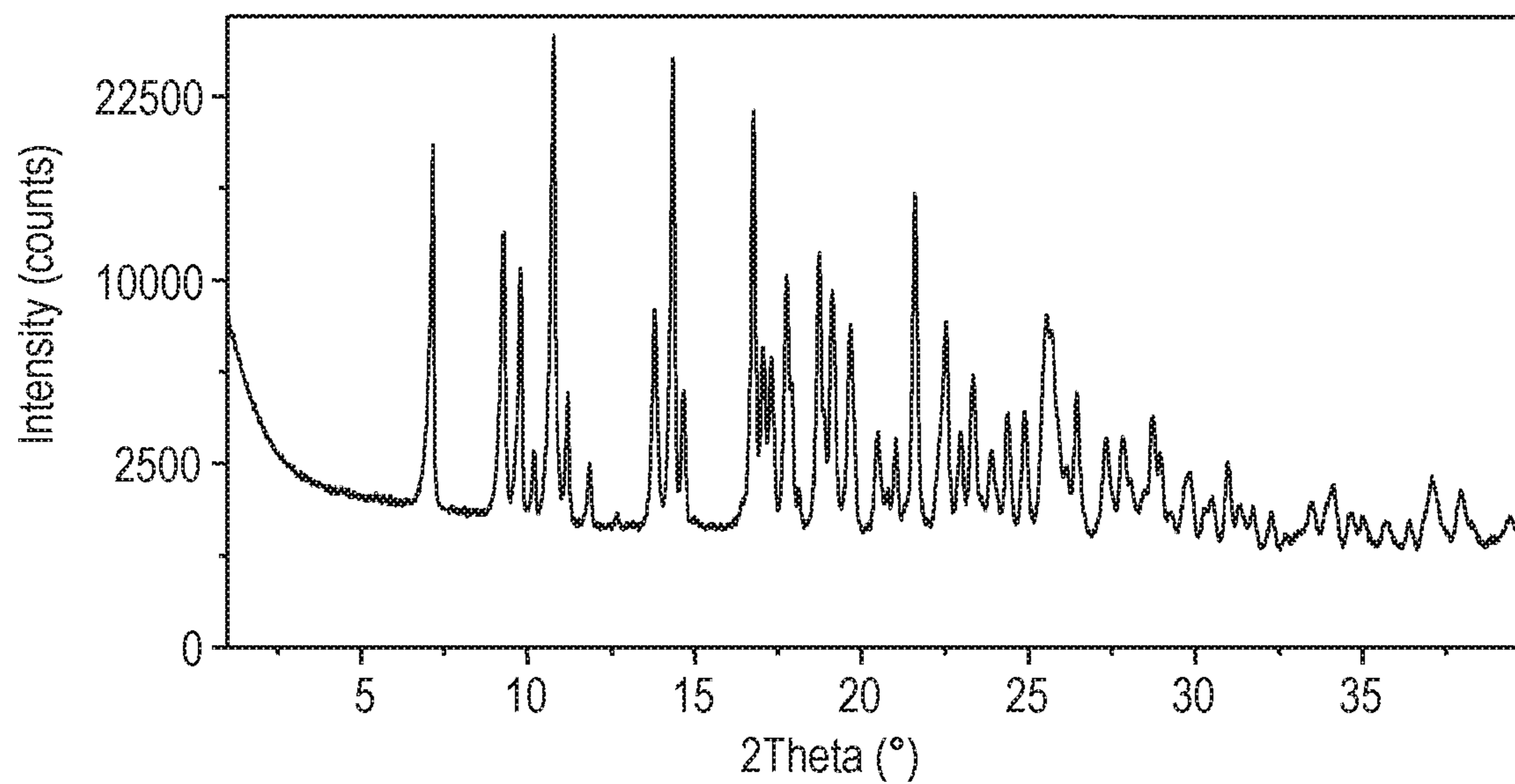


FIG. 54

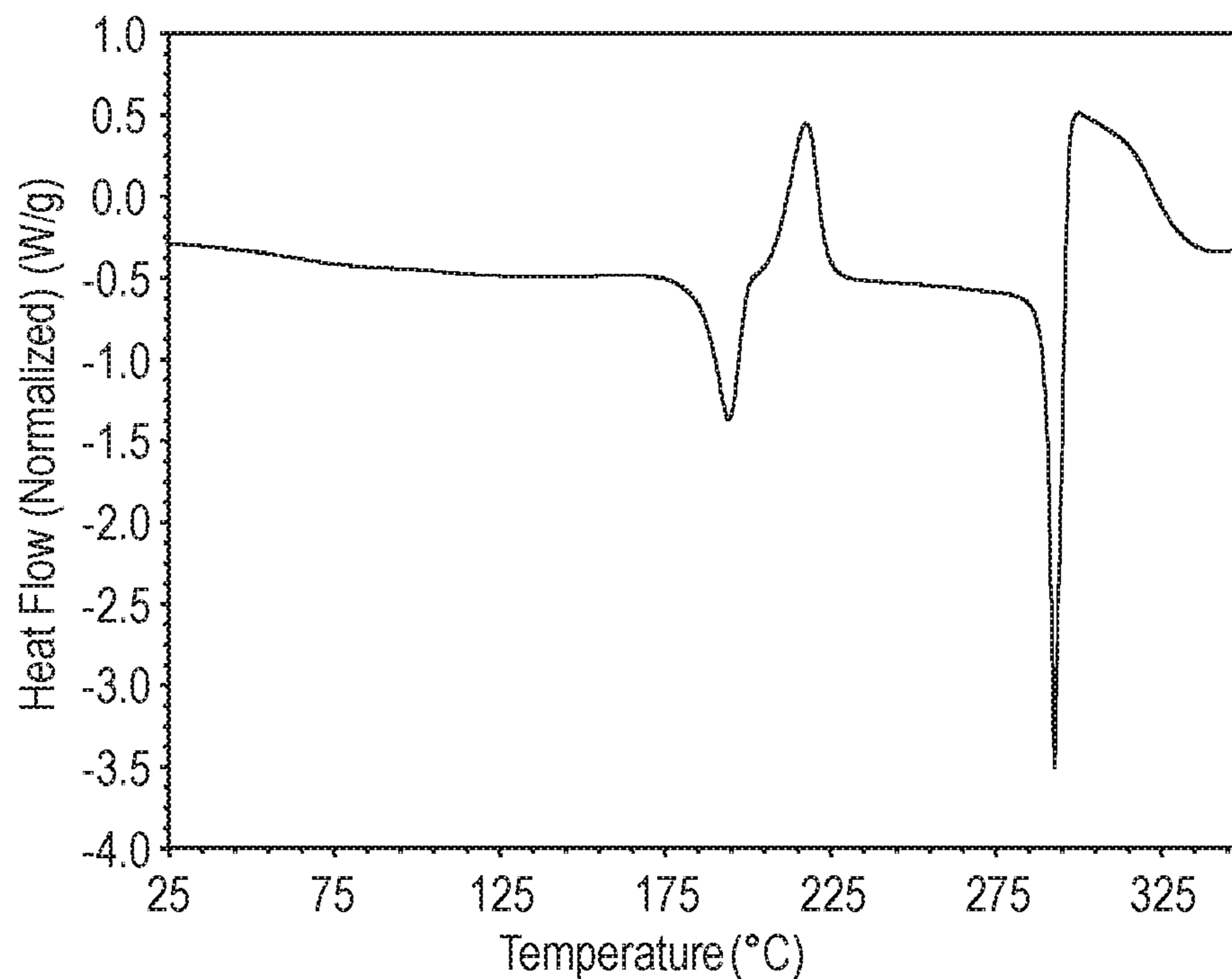


FIG. 55

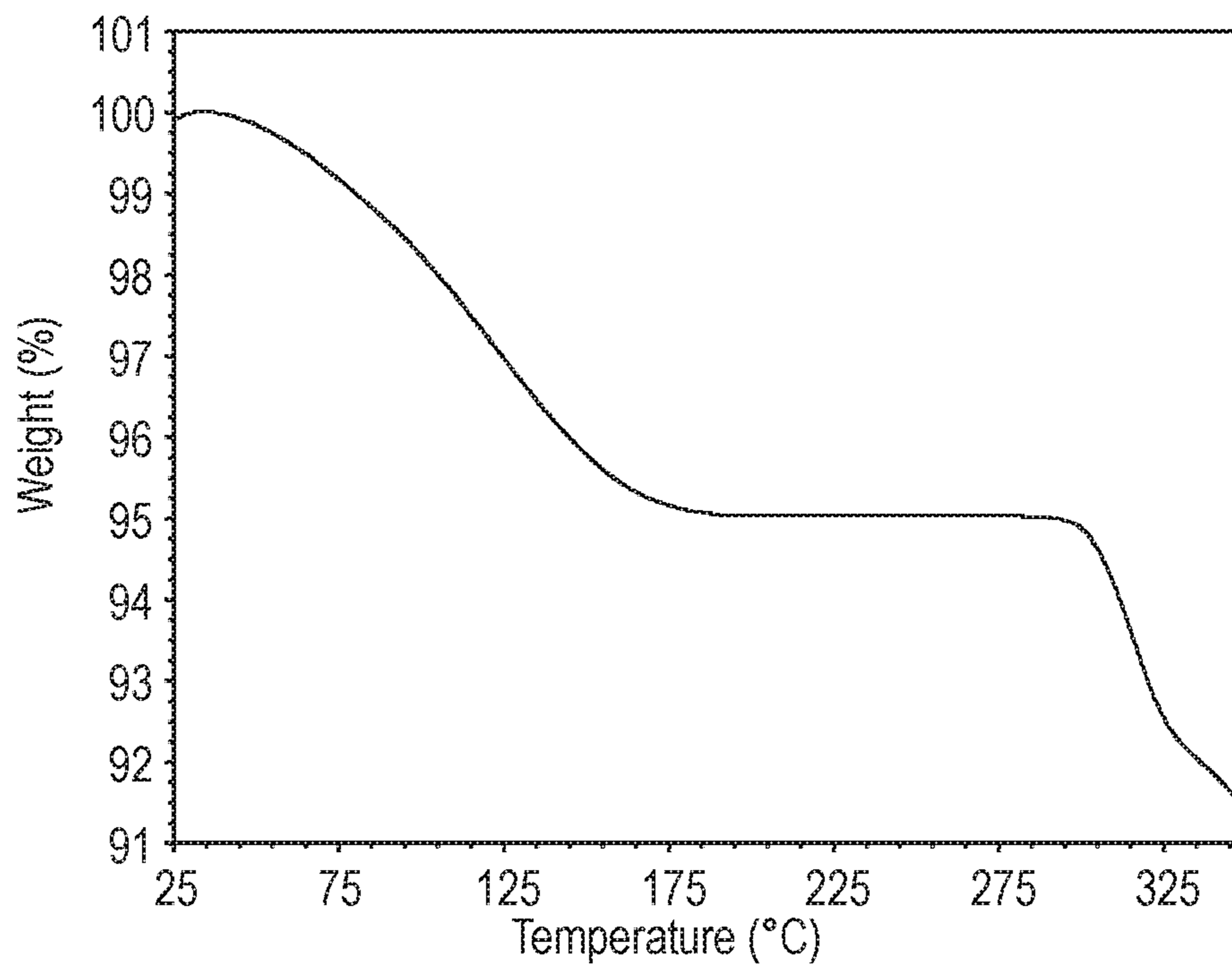
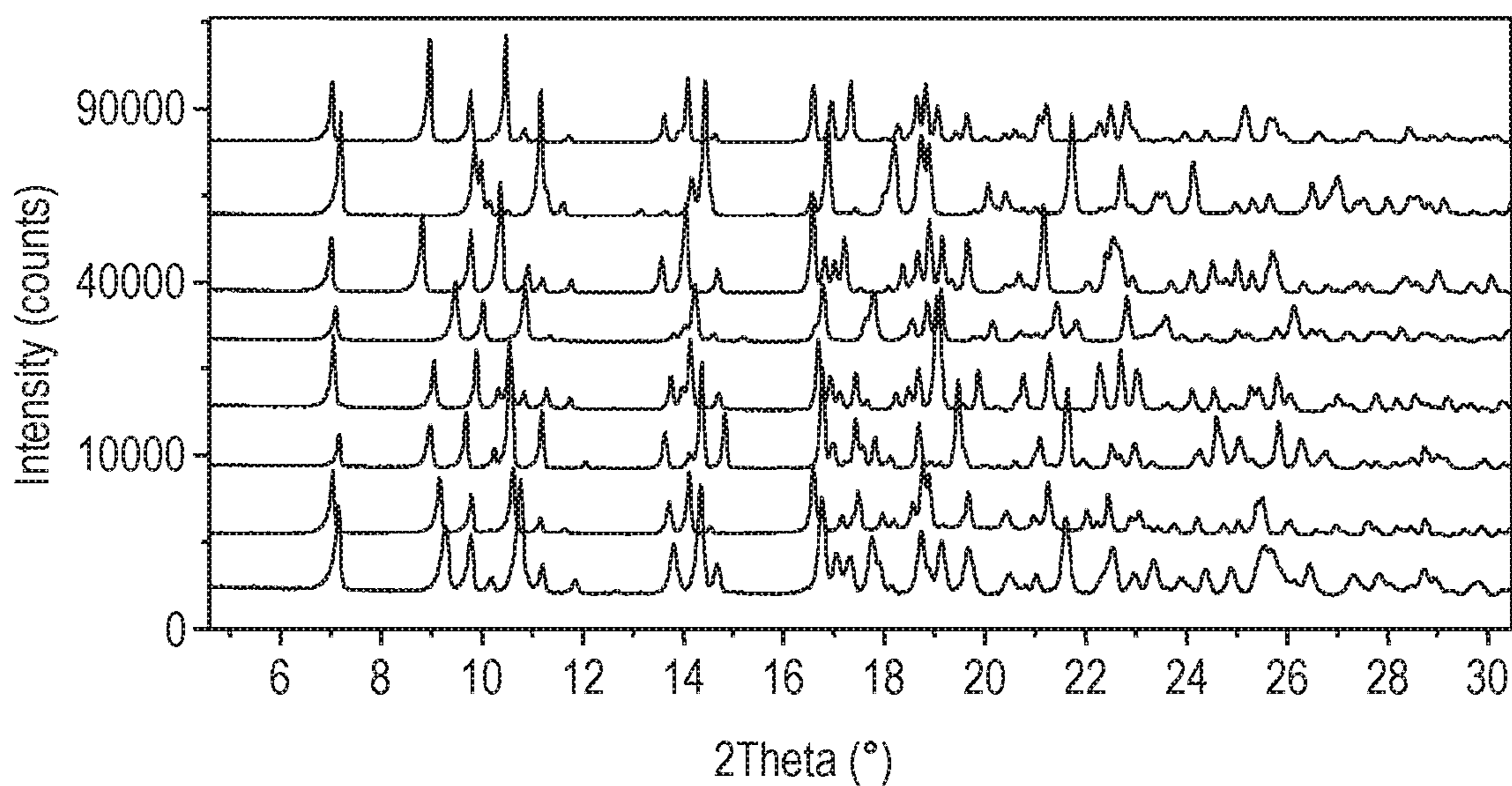


FIG. 56



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SOLID STATE FORMS

CROSS REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/878,824, filed May 20, 2020, which claims the benefit of U.S. Provisional Application No. 62/851,044, filed on May 21, 2019, all of which are incorporated herein by reference in their entireties.

FIELD

The present disclosure provides a crystalline form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, (hereinafter "Compound 1"), including several crystalline forms of an anhydrous form, a hydrate form, several solvate forms, and physical forms thereof, pharmaceutical compositions, and a method of treating a disease mediated by KRAS G12C inhibition.

BACKGROUND

Compound 1 is a selective inhibitor of KRAS G12C useful for the treatment of cancers, including treatment of lung cancer, such as non-small cell lung cancer (NSCLC), pancreatic cancer, and colorectal cancer. United States Patent Application Publication Number 2018/0334454A1, published on Nov. 22, 2018, discloses Compound 1.

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.*, 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions. This is particularly important from a regulatory standpoint, since drugs are approved by agencies such as the U.S. Food and Drug Administration only if they meet exacting purity and characterization standards. Indeed, the regulatory approval of one polymorph of a compound, which exhibits certain solubility and physico-chemical (including spectroscopic) properties, typically does not imply the ready approval of other polymorphs of that same compound.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries*, 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

The present disclosure provides new polymorphic forms of Compound 1, including several crystalline forms of an anhydrous form, a hydrate form, several solvate forms, and physical forms thereof, pharmaceutical compositions, and a method of treating a disease mediated by KRAS G12C inhibition. The new polymorphic forms can further the development of formulations for the treatment of these chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

SUMMARY

The present disclosure provides crystalline and amorphous forms of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-

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(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one, including several anhydrous, hydrate and solvate forms, and solid state forms thereof, pharmaceutical compositions, and methods of treating a disease mediated by KRAS G12C inhibition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows XRPD data for an amorphous form of Compound 1. The powder X-ray pattern is characteristic of amorphous material with a broad amorphous halo and no distinct compound related diffraction peaks from 5-40° 2-theta.

FIG. 2 shows DSC data for an amorphous form of Compound 1.

FIG. 3 shows TGA data for an amorphous form of Compound 1.

FIG. 4 shows ¹⁹F solid state NMR (SSNMR) for an amorphous form of Compound 1.

FIG. 5 shows XRPD data for the crystalline anhydrous form I of Compound 1. The powder X-ray diffraction pattern of the anhydrous forms I-III of Compound 1 is characteristic of crystalline material with distinct diffraction peaks between 3° 2-theta to 40° 2-theta.

FIG. 6 shows DSC data for crystalline anhydrous form I of Compound 1.

FIG. 7 shows TGA data for crystalline anhydrous form I of Compound 1.

FIG. 8 shows ¹³C SSNMR data for crystalline anhydrous form I of Compound 1.

FIG. 9 shows ¹⁹F SSNMR data for crystalline anhydrous form I of Compound 1.

FIG. 10 shows XRPD data for the crystalline anhydrous form II of Compound 1.

FIG. 11 shows DSC data for crystalline anhydrous form II of Compound 1.

FIG. 12 shows TGA data for crystalline anhydrous form II of Compound 1.

FIG. 13 shows ¹³C SSNMR data for crystalline anhydrous form II of Compound 1.

FIG. 14 shows ¹⁹F SSNMR data for crystalline anhydrous form II of Compound 1.

FIG. 15 shows XRPD data for the crystalline anhydrous form III of Compound 1.

FIG. 16 shows DSC data for crystalline anhydrous form III of Compound 1.

FIG. 17 shows TGA data for crystalline anhydrous form III of Compound 1.

FIG. 18 shows XRPD data for the crystalline hydrate form of Compound 1.

FIG. 19 shows DSC data for the crystalline hydrate form of Compound 1.

FIG. 20 shows TGA data for the crystalline hydrate form of Compound 1.

FIG. 21 is the overlay XRPD data (from top to bottom) for the crystalline anhydrous forms I, II, and III and the crystalline hydrate form of Compound 1.

FIG. 22 shows XRPD data for the crystalline THF Solvate Form I of Compound 1.

FIG. 23 shows DSC data for the crystalline THF Solvate Form I of Compound 1.

FIG. 24 shows TGA data for the crystalline THE Solvate Form I of Compound 1.

FIG. 25 shows XRPD data for the crystalline MeCN Solvate Form I of Compound 1.

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FIG. 26 shows DSC data for the crystalline MeCN Solvate Form I of Compound 1.

FIG. 27 shows TGA data for the crystalline MeCN Solvate Form I of Compound 1.

FIG. 28 shows XRPD data for the crystalline MEK Solvate Form I of Compound 1.

FIG. 29 shows DSC data for the crystalline MEK Solvate Form I of Compound 1.

FIG. 30 shows TGA data for the crystalline MEK Solvate Form I of Compound 1.

FIG. 31 shows XRPD data for the crystalline EtOAc Solvate Form I of Compound 1.

FIG. 32 shows XRPD data for the crystalline DMF Solvate Form I of Compound 1.

FIG. 33 shows DSC data for the crystalline DMF Solvate Form I of Compound 1.

FIG. 34 shows TGA data for the crystalline DMF Solvate Form I of Compound 1.

FIG. 35 shows XRPD data for the crystalline DCM Solvate Form I of Compound 1.

FIG. 36 shows DSC data for the crystalline DCM Solvate Form I of Compound 1.

FIG. 37 shows TGA data for the crystalline DCM Solvate Form I of Compound 1.

FIG. 38 shows XRPD data for the crystalline Acetone Solvate Form I of Compound 1.

FIG. 39 shows DSC data for the crystalline Acetone Solvate Form I of Compound 1.

FIG. 40 shows TGA data for the crystalline Acetone Solvate Form I of Compound 1.

FIG. 41 shows XRPD data for the crystalline Acetone Solvate Form II of Compound 1.

FIG. 42 shows DSC data for the crystalline Acetone Solvate Form II of Compound 1.

FIG. 43 shows TGA data for the crystalline Acetone Solvate Form II of Compound 1.

FIG. 44 shows XRPD data for the crystalline p-Dioxane Solvate Form I of Compound 1.

FIG. 45 shows DSC data for the crystalline p-Dioxane Solvate Form I of Compound 1.

FIG. 46 shows TGA data for the crystalline p-Dioxane Solvate Form I of Compound 1.

FIG. 47 shows XRPD data for the crystalline MeOH Solvate Form I of Compound 1.

FIG. 48 shows DSC data for the crystalline MeOH Solvate Form I of Compound 1.

FIG. 49 shows TGA data for the crystalline MeOH Solvate Form I of Compound 1.

FIG. 50 shows XRPD data for the crystalline IPA Solvate Form I of Compound 1.

FIG. 51 shows DSC data for the crystalline IPA Solvate Form I of Compound 1.

FIG. 52 shows TGA data for the crystalline IPA Solvate Form I of Compound 1.

FIG. 53 shows XRPD data for the crystalline EtOH Solvate Form I of Compound 1.

FIG. 54 shows DSC data for the crystalline EtOH Solvate Form I of Compound 1.

FIG. 55 shows TGA data for the crystalline EtOH Solvate Form I of Compound 1.

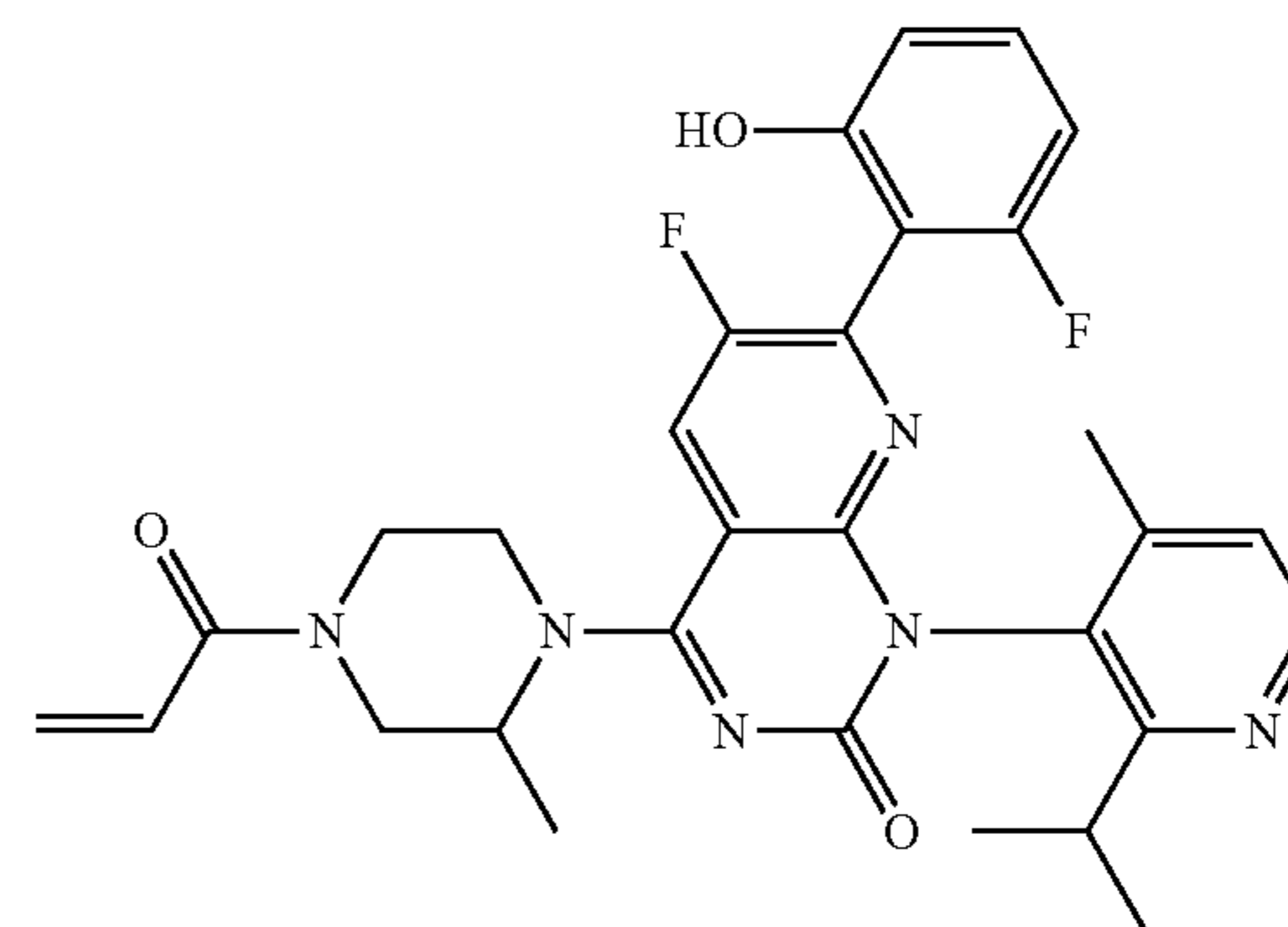
4

FIG. 56 is the overlay XRPD data for the isostructural solvate forms of Compound 1 (Top to bottom—THF, MeCN, MEK, DCM, acetone, MeOH, IPA, EtOH).

DETAILED DESCRIPTION

Definitions

The term “Compound 1” means 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one.



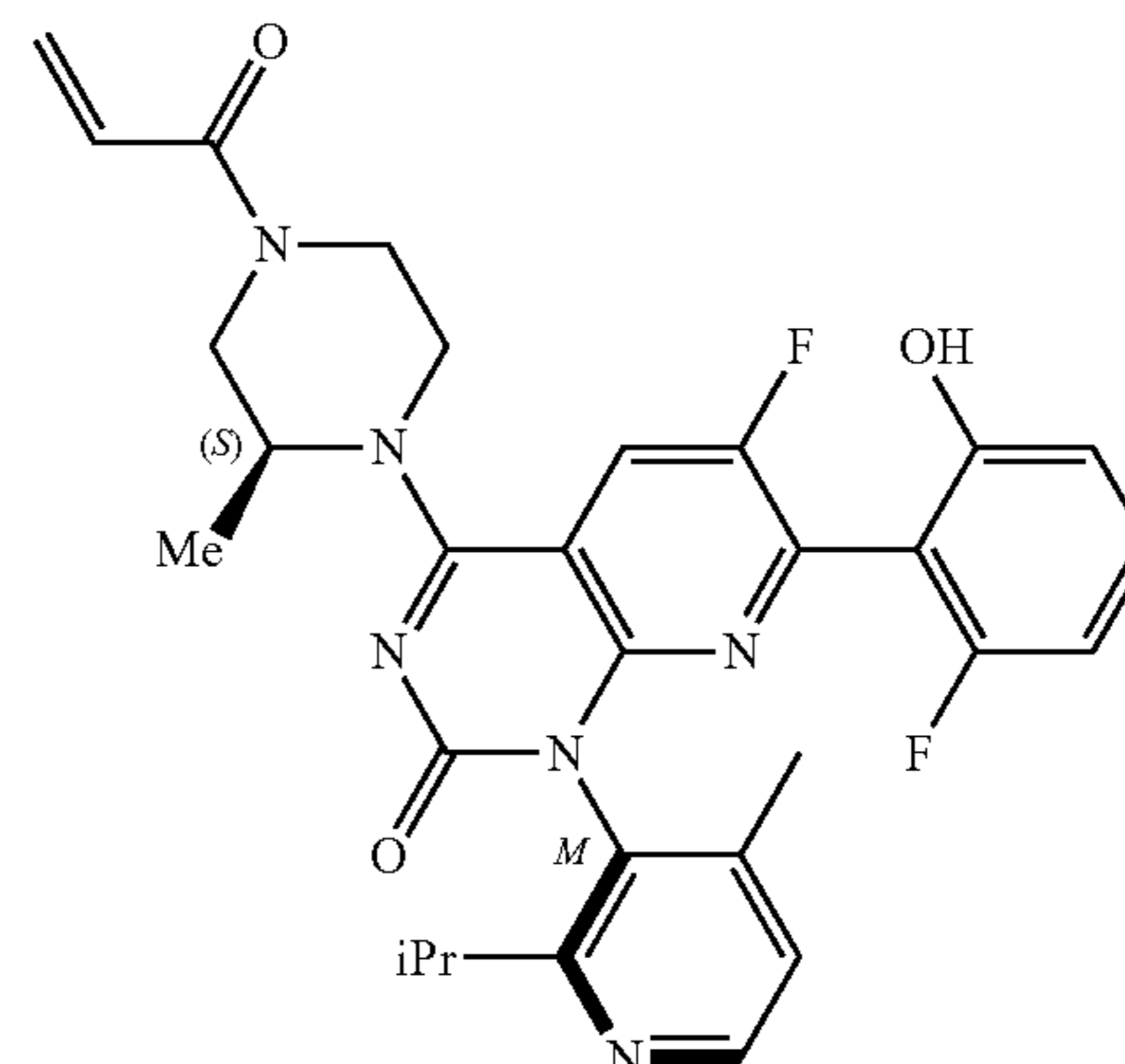
Chemical Formula: $C_{30}H_{30}F_2N_6O_3$

Exact Mass: 560.23

Molecular Weight: 560.61

Elemental Analysis: C, 64.28; H, 5.39; F, 6.78; N, 14.99; O, 8.56

Certain of the compounds disclosed herein may exist as atropisomers, which are conformational stereoisomers that occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule. The compounds disclosed herein include all atropisomers, both as pure individual atropisomer preparations, enriched preparations of each, or a non-specific mixture of each. Where the rotational barrier about the single bond is high enough, and interconversion between conformations is slow enough, separation and isolation of the isomeric species may be permitted. For example, Compound 1 is



atropisomer M and may exhibit restricted rotation. The M-atropisomer of Compound 1 is also known as AMG 510. Canon, J., et al., *Nature* 575(7781):217-223 (2019), FIG. 1a.

Alternatively, Compound 1 has the following atropisomer P and may exhibit restricted rotation.

anti-tumor efficacy of chemotherapy and targeted agents. Id. In immune-competent mice, treatment with AMG 510 resulted in a pro-inflammatory tumor microenvironment and produced durable cures alone as well as in combination with immune-checkpoint inhibitors. Id. Cured mice rejected the growth of isogenic KRAS^{G12D} tumors, which suggests adaptive immunity against shared antigens. Id. Furthermore, in clinical trials, AMG 510 demonstrated anti-tumor activity in the first dosing cohorts and represents a potentially transformative therapy for patients for whom effective treatments are lacking. Id.

The term “cancer” means a hyperproliferative disorder in a mammal, such as a human, with a KRAS, HRAS or NRAS G12C mutation, which can be treated by, for example, by administering to said mammal a therapeutically effective amount of Compound 1 as disclosed herein. In some embodiments, the cancer is, for example, acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related cancers (e.g. Lymphoma and Kaposi’s Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urachal cancer, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or viral-induced cancer. In some embodiments, said method relates to the treatment of

a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

The term “patient” means animals, such as dogs, cats, cows, horses, sheep and humans. Particular patients are mammals. The term patient includes males and females.

The term “therapeutically effective amount” means an amount of a compound that ameliorates, attenuates or eliminates one or more symptom of a particular disease or condition, or prevents or delays the onset of one of more symptoms of a particular disease or condition.

The term “pharmaceutically acceptable” means that the referenced substance, such as a compound of the present disclosure or a formulation containing a compound of the present disclosure, or a particular excipient, are suitable for administration to a patient.

As used herein and unless otherwise indicated, the terms “polymorph” and “polymorphic form” refer to solid crystalline forms of a compound or complex. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (e.g., to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation. Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy, solution calorimetry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility, and rate of dissolution.

As used herein to refer to the spectra or data presented in graphical form (e.g., XRPD, IR, Raman and NMR spectra), and unless otherwise indicated, the term “peak” refers to a peak or other special feature that one skilled in the art would recognize as not attributable to background noise.

As used herein and unless otherwise indicated, the term “substantially pure” when used to describe a polymorph of a compound means a solid form of the compound that comprises that polymorph and is substantially free of other polymorphs of the compound. A representative substantially pure polymorph comprises greater than about 80% by weight of one polymorphic form of the compound and less than about 20% by weight of other polymorphic forms of the

compound, more preferably greater than about 90% by weight of one polymorphic form of the compound and less than about 10% by weight of the other polymorphic forms of the compound, even more preferably greater than about 95% by weight of one polymorphic form of the compound and less than about 5% by weight of the other polymorphic forms of the compound, and most preferably greater than about 97% by weight of one polymorphic forms of the compound and less than about 3% by weight of the other polymorphic forms of the compound.

The terms "treating", "treat" or "treatment" and the like include preventative (e.g., prophylactic) and palliative treatment.

The term "variable hydrate" means a hydrate of Compound 1 having at least about one, two, three, or four associated water molecules. In some embodiments, the hydrates of the present disclosure include from at least one to ten associated molecules of water. Those skilled in the art appreciate that the exact number of the associated water molecules may vary slightly at any time with variable temperature, pressure, and other environmental influence. All slight variations of the number of the associated water molecules are contemplated to be within the scope of the present disclosure.

In some embodiments, the methods for treatment are directed to treating lung cancers, the methods comprise administering an effective amount of any of the above described compounds (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain embodiments the lung cancer is a non-small cell lung carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In some embodiments, the lung cancer is a small cell lung carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas. In one embodiment the NSCLC is locally advanced or metastatic.

The compounds of the present disclosure are administered to a patient in a therapeutically effective amount. The compounds can be administered alone or as part of a pharmaceutically acceptable composition or formulation. In addition, the compounds or compositions can be administered all at once, as for example, by a bolus injection, multiple times, such as by a series of tablets, or delivered substantially uniformly over a period of time, as for example, using transdermal delivery. It is also noted that the dose of the compound can be varied over time.

In addition, the compounds of the present disclosure can be administered alone, in combination with other compounds of the present disclosure, or with other pharmaceutically active compounds. The other pharmaceutically active compounds can be intended to treat the same disease or condition as the compounds of the present disclosure or a different disease or condition. If the patient is to receive or is receiving multiple pharmaceutically active compounds, the compounds can be administered simultaneously, or sequentially. For example, in the case of tablets, the active compounds may be found in one tablet or in separate tablets, which can be administered at once or sequentially in any order. In addition, it should be recognized that the compositions may be different forms. For example, one or more compound may be delivered via a tablet, while another is administered via injection or orally as a syrup. All combinations, delivery methods and administration sequences are contemplated.

It is also noted that the solid state forms of the present disclosure can be administered together. For example, sub-

stantially pure crystalline anhydrous form I of Compound 1 can be administered to a patient. Alternatively, about 90% by weight of crystalline anhydrous form I of Compound 1 can be administered with the remaining Compound 1 present in other forms, such as the amorphous form of Compound I. In another embodiment, 80% by weight of crystalline anhydrous form I of Compound 1 can be administered with the remaining Compound 1 present in other forms, such as the amorphous form. All combinations are contemplated. In one embodiment of the disclosure, Compound 1 is administered to a patient in one substantially pure form. Those skilled in the art will appreciate the possible variations.

The compounds of the present disclosure may be used in the manufacture of a medicament for the treatment of a disease mediated by KRAS G12C inhibition, such as cancer, including but not limited to colorectal cancer, pancreatic cancer and lung cancer, such as non-small cell lung cancer (NSCLC).

In still a further aspect, the disclosure relates to the use of a salt, a crystalline form, an amorphous form, or co-crystal of Compound 1 for the preparation of a medicament useful for treating cancer, such as colorectal cancer, pancreatic cancer and lung cancer, such as non-small cell lung cancer (NSCLC).

Since one aspect of the present disclosure contemplates the treatment of the disease/conditions with a combination of pharmaceutically active compounds that may be administered separately, the disclosure further relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of the present disclosure, and a second pharmaceutical compound. The kit comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes and bags. Typically, the kit comprises directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician or veterinarian.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week,

Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . .” etc. Other variations of memory aids will be readily apparent. A “daily dose” can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a compound of the present disclosure can consist of one tablet or capsule, while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this and aid in correct administration of the active agents.

In another specific embodiment of the disclosure, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered microchip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The compounds of the present disclosure and other pharmaceutically active compounds, if desired, can be administered to a patient either orally, rectally, parenterally, (for example, intravenously, intramuscularly, or subcutaneously) intracisternally, intravaginally, intraperitoneally, intravesically, locally (for example, powders, ointments or drops), or as a buccal or nasal spray. All methods that are used by those skilled in the art to administer a pharmaceutically active agent are contemplated. In one embodiment, the compounds of the present disclosure and other pharmaceutically active compounds, if desired, can be administered to a patient orally.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Microorganism contamination can be prevented by adding various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of injectable pharmaceutical compositions can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and

sodium carbonate; (a) solution retarders, as for example, paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, and tablets, the dosage forms may also comprise buffering agents. In one embodiment the dosage form contemplated in this disclosure is a solid dosage form, such as a tablet for oral administration.

Solid compositions of a similar type may also be used as fillers in hard filled gelatin capsules using such excipients as lactose, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs, for example in a soft filled gelatin capsules. In addition to the active compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. Suspensions, in addition to the active compound, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administration are preferable suppositories, which can be prepared by mixing the compounds of the present disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary room temperature, but liquid at body temperature, and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of the present disclosure include ointments, powders, sprays and inhalants. The active compound or fit compounds are admixed under sterile condition with a physiologically acceptable carrier, and any preservatives, buffers, or propellants that may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this disclosure.

The compounds of the present disclosure can be administered to a patient at dosage levels in the range of about 0.1

to about 2000 mg per day, preferably from 5 mg to 1000 mg per day. For a normal adult human having a body weight of about 70 kg, a dosage in the range of about 0.001 mg per kilogram body weight to about 20 mg per kilogram body weight is typically sufficient. The specific dosage and dosage range that can be used depends on a number of factors, including the requirements of the patient, the severity of the condition or disease being treated, and the pharmacological activity of the compound being administered. The determination of dosage ranges and optimal dosages for a particular patient is within the ordinary skill in the art. In one embodiment the total daily dose administered to a patient is 180 mg, 360 mg, 720 mg, or 960 mg. The total daily dose can be administered orally with multiple tablets containing, e.g., 120 mg of Compound 1 (e.g., the total daily dose of 960 mg is administered with 8 tablets of 120 mg of Compound 1 each). In one embodiment the total daily dose administered to a patient is 960 mg of Compound 1. In one embodiment the total daily dose of 960 mg of Compound 1 is administered with 8 tablets comprising 120 mg of Compound 1.

Unless specifically stated otherwise, the compounds of the present disclosure may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water (hydrate), ethanol, and the like. The present disclosure contemplates and encompasses both the solvated and unsolvated forms.

It is also possible that compounds of the present disclosure may exist in different tautomeric forms. All tautomers of compounds of the present disclosure are contemplated. For example, all keto-enol forms of the compounds are included in this disclosure.

Those skilled in the art will recognize that the compound names and structures contained herein may be based on a particular tautomer of a compound. While the name or structure for only a particular tautomer may be used, it is intended that all tautomers are encompassed by the present disclosure, unless stated otherwise.

Those skilled in the art will understand that the anhydrous free forms, hydrates, salts and co-crystals of Compound 1 may exist in one or more ionization states, which typically exists as zwitterions. While the name or structure for only a particular ionization state may be used, it is intended that all ionization states are encompassed by the present disclosure, unless stated otherwise.

It is also intended that the present disclosure encompasses compounds that are synthesized in vitro using laboratory techniques, such as those well known to synthetic chemists; or synthesized using in vivo techniques, such as through metabolism, fermentation, digestion, and the like. It is also contemplated that the compounds of the present disclosure may be synthesized using a combination of in vitro and in vivo techniques.

The present disclosure also includes isotopically-labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{16}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl .

Compounds of the present disclosure that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labelled compounds of the present disclosure, for example those into which radioactive isotopes such as ^3H

and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detection. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of this disclosure can generally be prepared by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

All patents and other publications recited herein are hereby incorporated by reference.

The examples and embodiments presented below are illustrative of the invention disclosed herein and are not intended to limit the scope of the claims in any manner.

EMBODIMENTS

1. In one embodiment, the present invent provides a crystalline anhydrous form I of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1).
2. In another embodiment, the present disclosure provides the crystalline anhydrous form I of embodiment 1, wherein the anhydrous form I is the M atropisomer.
3. In another embodiment, the present disclosure provides the crystalline anhydrous form I of embodiment 1, wherein the crystalline anhydrous form I is characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 5.
4. In another embodiment, the present disclosure provides the crystalline anhydrous form I of embodiment 1, wherein said crystalline anhydrous form I is characterized by at least three peaks, at least five peaks, or at least seven peaks selected from a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 8.8, 9.0, 10.8, 12.0, 12.6, 12.8, 13.6, 14.2, 15.0, 15.4, 18.0, 18.6, 18.7, 19.0, 19.9, 20.0, 22.9, and 25.0.
5. In another embodiment, the present disclosure provides the crystalline anhydrous form I of embodiment 1, wherein said crystalline anhydrous form I is characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 9.0, 12.0, 12.6 and 19.0.
6. In another embodiment, the present disclosure provides the crystalline anhydrous form I of embodiment 1 having a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 293° C.
7. In another embodiment, the present disclosure provides the crystalline anhydrous form of embodiment 1 having a thermogravimetric analysis thermogram comprising a weight loss of about 0.2% when heated from about 25° C. to about 275° C.
8. In another embodiment, the present disclosure provides the crystalline anhydrous form of embodiment 1, wherein said crystalline anhydrous form I is characterized by ^{13}C solid state NMR as depicted in FIG. 8.
9. In another embodiment, the present disclosure provides the crystalline anhydrous form of embodiment 1, wherein said crystalline anhydrous form I is characterized by ^{13}C solid state NMR, comprising peaks at approximately 12, 13, 16, 21, 23, 31, 33, 38, 42, 44, 47,

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- 50, 54, 107, 110, 111, 123, 124, 127, 128, 132, 145, 146, 150, 154, 156, 158, 160, 162, 166, 167.7 and 168 ppm.
10. In another embodiment, the present disclosure provides the crystalline anhydrous form of embodiment 1, wherein said crystalline anhydrous form I is characterized by ¹⁹F solid state NMR as depicted in FIG. 9. 5
11. In another embodiment, the present disclosure provides the crystalline anhydrous form of embodiment 1, wherein said crystalline anhydrous form I is characterized by ¹⁹F solid state NMR, comprising peaks at approximately -49, -60, -79, -90, -109, -120, -138, -150, -168 and -179 ppm. 10
12. In another embodiment, the present disclosure provides the crystalline anhydrous form of embodiment 1 which is substantially pure. 15
13. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline anhydrous form I of embodiment 1, and a pharmaceutically acceptable excipient. 20
14. In another embodiment, the present disclosure provides the pharmaceutical composition comprising the crystalline anhydrous form I as in any one of embodiments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, or a mixture thereof, and a pharmaceutically acceptable excipient. 25
15. In another embodiment, the present disclosure provides the pharmaceutical composition of embodiment 14, wherein the composition is a single dose.
16. In another embodiment, the present disclosure provides a composition comprising an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one and the crystalline anhydrous form I of embodiment 1. 30
17. In another embodiment, the present disclosure provides a method for preparing the crystalline anhydrous form I of embodiment 1, the method comprising: combining form II of Compound 1 and a suitable solvent, and removing the solvent to form a crystalline anhydrous form I of Compound 1. 40
18. In another embodiment, the present disclosure provides the method of embodiment 17, wherein the suitable solvent is water. 45
19. In another embodiment, the present disclosure provides a method of treating a disease mediated by KRAS G12C inhibition, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a pharmaceutical composition comprising the crystalline anhydrous form I of embodiment 1. 50
20. In another embodiment, the present disclosure provides a method of treating a disease mediated by KRAS G12C inhibition, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a pharmaceutical composition of embodiment 14. 55
21. In another embodiment, the present disclosure provides the method of embodiment 19, wherein said disease mediated by G12C inhibition is cancer. 60
22. In another embodiment, the present disclosure provides the method of embodiment 21, wherein the cancer is lung cancer, pancreatic cancer or colorectal cancer.
23. In another embodiment, the present disclosure provides the method of embodiment 22, wherein the cancer is lung cancer. 65

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24. In another embodiment, the present disclosure provides the method of embodiment 23, wherein the lung cancer is non-small cell lung cancer.
25. In another embodiment, the present disclosure provides an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one.
26. In another embodiment, the present disclosure provides the amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one of embodiment 25, characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 1.
27. In another embodiment, the present disclosure provides the amorphous form of embodiment 25, wherein the form is the M atropisomer.
28. In another embodiment, the present disclosure provides the amorphous form of embodiment 25 having a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 144° C.
29. In another embodiment, the present disclosure provides the amorphous form of embodiment 25 having a thermogravimetric analysis thermogram comprising a weight loss of about 1.5% when heated from about 25° C. to about 275° C.
30. In another embodiment, the present disclosure provides the amorphous form of embodiment 25, wherein said form is characterized by ¹⁹F solid state NMR as depicted in FIG. 4.
31. In another embodiment, the present disclosure provides the amorphous form of embodiment 25, wherein said form is characterized by ¹⁹F solid state NMR, comprising peaks at approximately -86, -96, -116, -127, -146 and -156 ppm.
32. In another embodiment, the present disclosure provides the amorphous form of embodiment 25 which is substantially pure.
33. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the amorphous form of embodiment 25, and a pharmaceutically acceptable excipient.
34. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the amorphous form as in any one of embodiments 25, 26, 27, 28, 29, 30, 31, 32 or 33, or a mixture thereof, and a pharmaceutically acceptable excipient.
35. In another embodiment, the present disclosure provides a pharmaceutical composition of embodiment 34, wherein the composition is a single dose.
36. In another embodiment, the present disclosure provides a method for preparing the amorphous form of embodiment 35, the method comprising dissolving Compound 1 and a suitable solvent to form an amorphous form of Compound 1.
37. In another embodiment, the present disclosure provides the method of embodiment 36 wherein the suitable solvent is methanol.
38. In another embodiment, the present disclosure provides a method of treating a disease mediated by KRAS G12C inhibition, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a pharmaceutical composition comprising the amorphous form of embodiment 25.

39. In another embodiment, the present disclosure provides the method of embodiment 38, wherein said disease mediated by G12C inhibition is cancer.
40. In another embodiment, the present disclosure provides the method of embodiment 39, wherein the cancer is lung cancer, pancreatic cancer or colorectal cancer.
41. In another embodiment, the present disclosure provides the method of embodiment 40, wherein the cancer is lung cancer.
42. In another embodiment, the present disclosure provides the method of embodiment 41, wherein the lung cancer is non-small cell lung cancer.
43. In another embodiment, the present disclosure provides a crystalline anhydrous form II of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1).
44. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43, wherein the anhydrous form II is the M atropisomer.
45. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43, characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 10.
46. In another embodiment, the present disclosure provides the crystalline anhydrous form II of Compound 1 of embodiment 43, wherein said form is characterized by at least three peaks, at least five peaks, or at least seven peaks selected from a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 7.3, 9.8, 10.1, 10.4, 11.3, 11.5, 11.9, 13.3, 14.3, 14.7, 17.2, and 18.4.
47. In another embodiment, the present disclosure provides the crystalline anhydrous form II of Compound II of embodiment 43, wherein said form is characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 7.3, 9.8, 10.1, 11.3, 13.3 and 17.2.
48. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43 having a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 193° C.
49. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43 having a thermogravimetric analysis thermogram comprising a weight loss of about 1% to about 1.8% when heated from about 25° C. to about 250° C.
50. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43, wherein said form is characterized by ¹³C solid state NMR as depicted in FIG. 13.
51. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43, wherein said form is characterized by ¹³C solid state NMR, comprising peaks at approximately 16, 18, 19, 20, 23, 25, 31, 32, 38, 40, 43, 46, 51, 57, 105, 107, 110, 117, 120, 123, 124, 125, 128, 132, 149, 152, 155, 158, 159, 163 and 166 ppm.
52. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43, wherein said form is characterized by ¹⁹F solid state NMR as depicted in FIG. 14.

53. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43, wherein said form is characterized by ¹⁹F solid state NMR, comprising peaks at approximately -59, -62, -89, -92, -119, -122, -148, -151, -179 and -181 ppm.
54. In another embodiment, the present disclosure provides the crystalline anhydrous form II of embodiment 43 which is substantially pure.
55. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline anhydrous form II of embodiment 43, and a pharmaceutically acceptable excipient.
56. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline anhydrous form II as in any one of embodiments 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54 or 55, or a mixture thereof, and a pharmaceutically acceptable excipient.
57. In another embodiment, the present disclosure provides the pharmaceutical composition of embodiment 56, wherein the composition is a single dose.
58. In another embodiment, the present disclosure provides the composition comprising an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one and the crystalline anhydrous form II of embodiment 43.
59. In another embodiment, the present disclosure provides a method for preparing the crystalline anhydrous form II of embodiment 43, the method comprising: combining an amorphous form of Compound 1 and a suitable solvent to form a crystalline anhydrous form II of Compound 1.
60. In another embodiment, the present disclosure provides the method of embodiment 59 wherein the suitable solvent is methanol.
61. In another embodiment, the present disclosure provides a method of treating a disease mediated by KRAS G12C inhibition, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a pharmaceutical composition comprising the crystalline anhydrous form II of embodiment 43.
62. In another embodiment, the present disclosure provides the method of embodiment 61, wherein said disease mediated by G12C inhibition is cancer.
63. In another embodiment, the present disclosure provides the method of embodiment 62, wherein the cancer is lung cancer, pancreatic cancer or colorectal cancer.
64. In another embodiment, the present disclosure provides the method of embodiment 63, wherein the cancer is lung cancer.
65. In another embodiment, the present disclosure provides the method of embodiment 64, wherein the lung cancer is non-small cell lung cancer.
66. In another embodiment, the present disclosure provides a crystalline anhydrous form III of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1).
67. In another embodiment, the present disclosure provides the crystalline anhydrous form III of embodiment 66, wherein the anhydrous form III is the M atropisomer.

68. In another embodiment, the present disclosure provides the crystalline anhydrous form III of embodiment 66, characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 15.
69. In another embodiment, the present disclosure provides the crystalline anhydrous form III of Compound 1 of embodiment 66, wherein said form is characterized by at least three peaks, at least five peaks, or at least seven peaks selected from a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 6.3, 8.4, 9.5, 10.4, 14.9, 15.4, 15.5, 16.0, and 17.6.
70. In another embodiment, the present disclosure provides the crystalline anhydrous form III of Compound II of embodiment 66, wherein said form is characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 6.3, 8.4, 9.5, 15.5, and 16.0.
71. In another embodiment, the present disclosure provides the crystalline anhydrous form III of embodiment 66 having a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 194° C.
72. In another embodiment, the present disclosure provides the crystalline anhydrous form III of embodiment 66 having a thermogravimetric analysis thermogram comprising an approximate negligible weight loss when heated from about 25° C. to about 250° C.
73. In another embodiment, the present disclosure provides the crystalline anhydrous form III of embodiment 66 which is substantially pure.
74. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline anhydrous form III of embodiment 66, and a pharmaceutically acceptable excipient.
75. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline anhydrous form III as in any one of embodiments 66, 67, 68, 69, 70, 71, 72, 73 or 74, or a mixture thereof, and a pharmaceutically acceptable excipient.
76. In another embodiment, the present disclosure provides the pharmaceutical composition of embodiment 75, wherein the composition is a single dose.
77. In another embodiment, the present disclosure provides a composition comprising an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one and the crystalline anhydrous form III of embodiment 66.
78. In another embodiment, the present disclosure provides a method for preparing the crystalline anhydrous form III of embodiment 66, the method comprising: combining Compound 1 and a suitable solvent to form a crystalline anhydrous form III of Compound 1.
79. In another embodiment, the present disclosure provides the method of embodiment 78 wherein the suitable solvent is acetone.
80. In another embodiment, the present disclosure provides a method of treating a disease mediated by KRAS G12C inhibition, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a pharmaceutical composition comprising the crystalline anhydrous form III of embodiment 66.
81. In another embodiment, the present disclosure provides the method of embodiment 80, wherein said disease mediated by G12C inhibition is cancer.

82. In another embodiment, the present disclosure provides the method of embodiment 81, wherein the cancer is lung cancer, pancreatic cancer or colorectal cancer.
83. In another embodiment, the present disclosure provides the method of embodiment 82, wherein the cancer is lung cancer.
84. In another embodiment, the present disclosure provides the method of embodiment 82, wherein the lung cancer is non-small cell lung cancer.
85. In another embodiment, the present disclosure provides a crystalline hydrate form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1).
86. In another embodiment, the present disclosure provides the crystalline hydrate form of embodiment 85, wherein the hydrate form is the M atropisomer.
87. In another embodiment, the present disclosure provides the crystalline hydrate form of embodiment 85, characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 18.
88. In another embodiment, the present disclosure provides the crystalline hydrate form of Compound 1 of embodiment 85, wherein said form is characterized by at least three peaks, at least five peaks, or at least seven peaks selected from a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 4.0, 4.4, 4.8, 6.9, 8.0, 8.8, 9.6, 11.3, 12.4, 13.0, 13.1, 14.6, 14.9, 15.2, 16.2, 16.4, 16.6, 17.3, 17.4, 17.9, and 19.5.
89. In another embodiment, the present disclosure provides the crystalline hydrate form of Compound I of embodiment 85, wherein said form is characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 6.9, 8.0, 9.6, 12.4, and 13.1.
90. In another embodiment, the present disclosure provides the crystalline hydrate form of embodiment 85 having a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 91° C.
91. In another embodiment, the present disclosure provides the crystalline hydrate form of embodiment 85 having a thermogravimetric analysis thermogram comprising an approximate 11% weight loss when heated from about 39° C. to about 160° C.
92. In another embodiment, the present disclosure provides the crystalline hydrate form of embodiment 85 which is substantially pure.
93. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline hydrate form of embodiment 85, and a pharmaceutically acceptable excipient.
94. In another embodiment, the present disclosure provides a pharmaceutical composition comprising the crystalline hydrate form as in any one of embodiments 85, 86, 87, 88, 89, 90, 91, 92 or 93, or a mixture thereof, and a pharmaceutically acceptable excipient.
95. In another embodiment, the present disclosure provides the pharmaceutical composition of embodiment 94, wherein the composition is a single dose.
96. In another embodiment, the present disclosure provides a composition comprising an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propanyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-pro-

- penoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one and the crystalline hydrate form of embodiment 85.
97. In another embodiment, the present disclosure provides a method for preparing the crystalline hydrate form of embodiment 85, the method comprising: combining Compound 1 and a suitable solvent in the presence of water to form a crystalline hydrate form of Compound 1.
98. In another embodiment, the present disclosure provides the method of embodiment 78 wherein the suitable solvent is methanol.
99. In another embodiment, the present disclosure provides a method of treating a disease mediated by KRAS G12C inhibition, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of a pharmaceutical composition comprising the crystalline hydrate form of embodiment 85.
100. In another embodiment, the present disclosure provides the method of embodiment 99, wherein said disease mediated by G12C inhibition is cancer.
101. In another embodiment, the present disclosure provides the method of embodiment 100, wherein the cancer is lung cancer, pancreatic cancer or colorectal cancer.
102. In another embodiment, the present disclosure provides the method of embodiment 101, wherein the cancer is lung cancer.
103. In another embodiment, the present disclosure provides the method of embodiment 102, wherein the lung cancer is non-small cell lung cancer.
104. In another embodiment, the present disclosure provides a crystalline solvate form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1).
105. In another embodiment, the present disclosure provides the crystalline solvate form of embodiment 104, wherein the solvate form is a THF, MeCN, MEK, EtOAc, DCM, acetone, p-dioxane, methanol, isopropyl alcohol, or ethanol solvate form.
106. In another embodiment, the present disclosure provides a pharmaceutical composition comprising an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one and at least one crystalline form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one of any one of embodiments 1, 43, 66, 85 or 104 and a pharmaceutically acceptable excipient.
107. In another embodiment, the present disclosure provides the composition of embodiment 106, which comprises greater than about 50 weight percent crystalline 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one.
108. In another embodiment, the present disclosure provides a pharmaceutical composition comprising at least one crystalline form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one of any one of embodiments 1, 43, 66, 85 or 104 and a pharmaceutically acceptable excipient.

ALTERNATIVE EMBODIMENTS

- Provided herein as Embodiment 1 is a compound, wherein the compound is a crystalline form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1) or an atropisomer thereof.
- Provided herein as Embodiment 2 is the compound of Embodiment 1, wherein the compound is the M atropisomer of Compound 1.
- Provided herein as Embodiment 3 is the compound of Embodiment 1 or 2, wherein the compound is a crystalline anhydrous form of Compound 1.
- Provided herein as Embodiment 4 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 9.0, 12.0, 12.6, and 19.0 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.
- Provided herein as Embodiment 5 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least three peaks selected from 8.8, 9.0, 10.8, 12.0, 12.6, 12.8, 13.6, 14.2, 15.0, 15.4, 18.0, 18.6, 18.7, 19.0, 19.9, 20.0, 22.9, and 25.0 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.
- Provided herein as Embodiment 6 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least five peaks selected from 8.8, 9.0, 10.8, 12.0, 12.6, 12.8, 13.6, 14.2, 15.0, 15.4, 18.0, 18.6, 18.7, 19.0, 19.9, 20.0, 22.9, and 25.0 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.
- Provided herein as Embodiment 7 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least seven peaks selected from 8.8, 9.0, 10.8, 12.0, 12.6, 12.8, 13.6, 14.2, 15.0, 15.4, 18.0, 18.6, 18.7, 19.0, 19.9, 20.0, 22.9, and 25.0 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.
- Provided herein as Embodiment 8 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 8.8, 9.0, 10.8, 12.0, 12.6, 12.8, 13.6, 14.2, 15.0, 15.4, 18.0, 18.6, 18.7, 19.0, 19.9, 20.0, 22.9, and 25.0 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.
- Provided herein as Embodiment 9 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 5 as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.
- Provided herein as Embodiment 10 is the compound of any one of Embodiments 1-9, wherein the compound is characterized by a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 293° C.
- Provided herein as Embodiment 11 is the compound of any one of Embodiments 1-10, wherein the compound is characterized by a thermogravimetric analysis thermogram comprising a weight loss of about 0.2% when heated from about 25° C. to about 275° C.
- Provided herein as Embodiment 12 is the compound of any one of Embodiments 1-11, wherein the compound is characterized by ^{13}C solid state NMR comprising at least three peaks selected from peaks at approximately 12, 13, 16,

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21, 23, 31, 33, 38, 42, 44, 47, 50, 54, 107, 110, 111, 123, 124, 127, 128, 132, 145, 146, 150, 154, 156, 158, 160, 162, 166, 167, and 168 ppm.

Provided herein as Embodiment 13 is the compound of any one of Embodiments 1-11, wherein the compound is characterized by ^{13}C solid state NMR comprising at least five peaks selected from peaks at approximately 12, 13, 16, 21, 23, 31, 33, 38, 42, 44, 47, 50, 54, 107, 110, 111, 123, 124, 127, 128, 132, 145, 146, 150, 154, 156, 158, 160, 162, 166, 167, and 168 ppm.

Provided herein as Embodiment 14 is the compound of any one of Embodiments 1-11, wherein the compound is characterized by ^{13}C solid state NMR comprising at least seven peaks selected from peaks at approximately 12, 13, 16, 21, 23, 31, 33, 38, 42, 44, 47, 50, 54, 107, 110, 111, 123, 124, 127, 128, 132, 145, 146, 150, 154, 156, 158, 160, 162, 166, 167, and 168 ppm.

Provided herein as Embodiment 15 is the compound of any one of Embodiments 1-11, wherein the compound is characterized by ^{13}C solid state NMR comprising peaks at approximately 12, 13, 16, 21, 23, 31, 33, 38, 42, 44, 47, 50, 54, 107, 110, 111, 123, 124, 127, 128, 132, 145, 146, 150, 154, 156, 158, 160, 162, 166, 167, and 168 ppm.

Provided herein as Embodiment 16 is the compound of any one of Embodiments 1-11, wherein the compound is characterized by ^{13}C solid state NMR substantially as depicted in FIG. 8.

Provided herein as Embodiment 17 is the compound of any one of Embodiments 1-16, wherein the compound is characterized by ^{19}F solid state NMR comprising peaks at approximately -49, -60, -79, -90, -109, -120, -138, -150, -168, and -179 ppm.

Provided herein as Embodiment 18 is the compound of any one of Embodiments 1-16, wherein the compound is characterized by ^{19}F solid state NMR substantially as depicted in FIG. 9.

Provided herein as Embodiment 19 is the compound of any one of Embodiments 1-18, wherein the compound is substantially pure.

Provided herein as Embodiment 20 is a pharmaceutical composition comprising the compound of any one of Embodiments 1-19 and a pharmaceutically acceptable excipient.

Provided herein as Embodiment 21 is the pharmaceutical composition of Embodiment 20, wherein the pharmaceutical composition is a dosage form for oral administration.

Provided herein as Embodiment 22 is the pharmaceutical composition of Embodiment 20 or 21, wherein the dosage form is a solid dosage form.

Provided herein as Embodiment 23 is the pharmaceutical composition of Embodiment 22, wherein the solid dosage form is a tablet.

Provided herein as Embodiment 24 is the pharmaceutical composition of any one of Embodiments 20-23, wherein the pharmaceutical composition comprises 120 mg of the compound.

Provided herein as Embodiment 25 is a compound of any one of Embodiments 1-19 or the pharmaceutical composition of any one of Embodiments 20-24 for use as a medicament.

Provided herein as Embodiment 26 is a compound of any one of Embodiments 1-19 or the pharmaceutical composition of any one of Embodiments 20-24 for use in treating cancer having a KRAS G12C mutation.

Provided herein as Embodiment 27 is the compound or the pharmaceutical composition for use of Embodiment 26,

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wherein the cancer having a KRAS G12C mutation is lung cancer, pancreatic cancer, or colorectal cancer.

Provided herein as Embodiment 28 is the compound or the pharmaceutical composition for use of Embodiment 26, wherein the cancer having a KRAS G12C mutation is non-small cell lung cancer.

Provided herein as Embodiment 29 is the compound or the pharmaceutical composition for use of Embodiment 26, wherein the cancer having a KRAS G12C mutation is pancreatic cancer.

Provided herein as Embodiment 30 is the compound or the pharmaceutical composition for use of Embodiment 26, wherein the cancer having a KRAS G12C mutation is colorectal cancer.

Provided herein as Embodiment 31 is a use of the compound of any one of Embodiments 1-19 or the pharmaceutical composition of any one of Embodiments 20-24 in the preparation of a medicament for treating cancer having a KRAS G12C mutation.

Provided herein as Embodiment 32 is the use of Embodiment 31, wherein the cancer having a KRAS G12C mutation is lung cancer, pancreatic cancer, or colorectal cancer.

Provided herein as Embodiment 33 is the use of Embodiment 31, wherein the cancer having a KRAS G12C mutation is non-small cell lung cancer.

Provided herein as Embodiment 34 is the use of Embodiment 31, wherein the cancer having a KRAS G12C mutation is pancreatic cancer.

Provided herein as Embodiment 35 is the use of Embodiment 31, wherein the cancer having a KRAS G12C mutation is colorectal cancer.

Provided herein as Embodiment 36 is a method of treating a cancer having a KRAS G12C mutation in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of Embodiments 1-19.

Provided herein as Embodiment 37 is the method of Embodiment 36, wherein the cancer having a KRAS G12C mutation is lung cancer, pancreatic cancer, or colorectal cancer.

Provided herein as Embodiment 38 is the method of Embodiment 36, wherein the cancer having a KRAS G12C mutation is small cell lung cancer.

Provided herein as Embodiment 39 is the method of Embodiment 36, wherein the cancer having a KRAS G12C mutation is pancreatic cancer.

Provided herein as Embodiment 40 is the method of Embodiment 36, wherein the cancer having a KRAS G12C mutation is colorectal cancer.

Provided herein as Embodiment 41 is the compound, use, or method of any one of Embodiments 25-40, wherein the compound is administered at a total daily dose of 960 mg.

Provided herein as Embodiment 42 is the compound, use, or method of any one of Embodiments 25-41, wherein the compound is administered to an adult.

Provided herein as Embodiment 43 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 7.3, 9.8, 10.1, 11.3, 13.3, and 17.2 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 44 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least three peaks selected from 7.3, 9.8, 10.1, 10.4,

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11.3, 11.5, 11.9, 13.3, 14.3, 14.7, 17.2, and 18.4 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 45 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least five peaks selected from 7.3, 9.8, 10.1, 10.4, 11.3, 11.5, 11.9, 13.3, 14.3, 14.7, 17.2, and 18.4 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 46 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least seven peaks selected from 7.3, 9.8, 10.1, 10.4, 11.3, 11.5, 11.9, 13.3, 14.3, 14.7, 17.2, and 18.4 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 47 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 7.3, 9.8, 10.1, 10.4, 11.3, 11.5, 11.9, 13.3, 14.3, 14.7, 17.2, and 18.4 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 48 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 10 as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 49 is the compound of any one of Embodiments 1-3 and 43-48, wherein the compound is characterized by a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 193° C.

Provided herein as Embodiment 50 is the compound of any one of Embodiments 1-3 and 43-49, wherein the compound is characterized by having a thermogravimetric analysis thermogram comprising a weight loss of about 1% to about 1.8% when heated from about 25° C. to about 250° C.

Provided herein as Embodiment 51 is the compound of any one of Embodiments 1-3 and 43-50, wherein the compound is characterized by ^{13}C solid state NMR comprising peaks at approximately 16, 18, 19, 20, 23, 25, 31, 32, 38, 40, 43, 46, 51, 57, 105, 107, 110, 117, 120, 123, 124, 125, 128, 132, 149, 152, 155, 158, 159, 163, and 166 ppm.

Provided herein as Embodiment 52 is the compound of any one of Embodiments 1-3 and 43-50, wherein the compound is characterized by ^{13}C solid state NMR substantially as depicted in FIG. 13.

Provided herein as Embodiment 53 is the compound of any one of Embodiments 1-3 and 43-52, wherein the compound is characterized by ^{19}F solid state NMR, comprising peaks at approximately -59, -62, -89, -92, -119, -122, -148, -151, -179 and -181 ppm.

Provided herein as Embodiment 54 is the compound of any one of Embodiments 1-3 and 43-52, wherein the compound is characterized by ^{19}F solid state NMR substantially as depicted in FIG. 14.

Provided herein as Embodiment 55 is the compound of any one of Embodiments 43-54, wherein the compound is substantially pure.

Provided herein as Embodiment 56 is a pharmaceutical composition comprising the compound of any one of Embodiments 43-55 and a pharmaceutically acceptable excipient.

Provided herein as Embodiment 57 is the compound of any one of Embodiments 1-3, wherein the compound is

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characterized by a powder X-ray diffraction pattern comprising peaks at 6.3, 8.4, 9.5, and 16.0 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 58 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least three peaks selected from 6.3, 8.4, 9.5, 10.4, 14.9, 15.4, 15.5, 16.0, and 17.6 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 59 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least five peaks selected from 6.3, 8.4, 9.5, 10.4, 14.9, 15.4, 15.5, 16.0, and 17.6 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 60 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least seven peaks selected from 6.3, 8.4, 9.5, 10.4, 14.9, 15.4, 15.5, 16.0, and 17.6 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 61 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 6.3, 8.4, 9.5, 10.4, 14.9, 15.4, 15.5, 16.0, and 17.6 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 62 is the compound of any one of Embodiments 1-3, wherein the compound is characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 15 as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 63 is the compound of any one of Embodiments 1-3 and 57-62, wherein the compound is characterized by a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 194° C.

Provided herein as Embodiment 64 is the compound of any one of Embodiments 1-3 and 57-63, wherein the compound is characterized by having an approximate negligible weight loss when heated from about 25° C. to about 250° C.

Provided herein as Embodiment 65 is the compound of any one of Embodiments 57-64, wherein the compound is substantially pure.

Provided herein as Embodiment 66 is a pharmaceutical composition comprising the compound of any one of Embodiments 57-65 and a pharmaceutically acceptable excipient.

Provided herein as Embodiment 67 is the compound of Embodiment 1 or 2, wherein the compound is a crystalline hydrate form of Compound 1.

Provided herein as Embodiment 68 is the compound of any one of Embodiments 1, 2, and 67, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 6.9, 8.0, 9.6, 12.4, and 13.1 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 69 is the compound of any one of Embodiments 1, 2, and 67, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least three peaks selected from 4.0, 4.4, 4.8, 6.9, 8.0, 8.8, 9.6, 11.3, 12.4, 13.0, 13.1, 14.6, 14.9, 15.2,

16.6, 17.3, 17.4, 17.9, and 19.5 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 70 is the compound of any one of Embodiments 1, 2, and 67, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least five peaks selected from 4.0, 4.4, 4.8, 6.9, 8.0, 8.8, 9.6, 11.3, 12.4, 13.0, 13.1, 14.6, 14.9, 15.2, 16.6, 17.3, 17.4, 17.9, and 19.5 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 71 is the compound of any one of Embodiments 1, 2, and 67, wherein the compound is characterized by a powder X-ray diffraction pattern comprising at least seven peaks selected from 4.0, 4.4, 4.8, 6.9, 8.0, 8.8, 9.6, 11.3, 12.4, 13.0, 13.1, 14.6, 14.9, 15.2, 16.6, 17.3, 17.4, 17.9, and 19.5 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 72 is the compound of any one of Embodiments 1, 2, and 67, wherein the compound is characterized by a powder X-ray diffraction pattern comprising peaks at 4.0, 4.4, 4.8, 6.9, 8.0, 8.8, 9.6, 11.3, 12.4, 13.0, 13.1, 14.6, 14.9, 15.2, 16.2, 16.4, 16.6, 17.3, 17.4, 17.9, and 19.5 ± 0.2 degrees 2 theta as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 73 is the compound of any one of Embodiments 1, 2, and 67, wherein the compound is characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 18 as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 74 is the compound of any one of Embodiments 1, 2, and 67-73, wherein the compound is characterized by a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 91° C.

Provided herein as Embodiment 75 is the compound of any one of Embodiments 1, 2, and 67-74, wherein the compound is characterized by having a thermogravimetric analysis thermogram comprising an approximate 11% weight loss when heated from about 39° C. to about 160° C.

Provided herein as Embodiment 76 is the compound of any one of Embodiments 67-75, wherein the compound is substantially pure.

Provided herein as Embodiment 77 is a pharmaceutical composition comprising the compound of any one of Embodiments 67-76 and a pharmaceutically acceptable excipient.

Provided herein as Embodiment 78 is the compound of Embodiment 1 or 2, wherein the compound is a crystalline solvate form of Compound 1.

Provided herein as Embodiment 79 is the compound of Embodiment 78, wherein the compound is a solvate with tetrahydrofuran, acetonitrile, methyl ethylketone, ethyl acetate, dichloromethane, acetone, p-dioxane, methanol, isopropyl alcohol, or ethanol.

Provided herein as Embodiment 80 is a compound, wherein the compound is an amorphous form of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1) or an atropisomer thereof.

Provided herein as Embodiment 81 is the compound of Embodiment 80, wherein the compound is the M atropisomer of Compound 1.

Provided herein as Embodiment 82 is the compound of Embodiments 80 or 81, wherein the compound is characterized by the powder X-ray diffraction pattern substantially as shown in FIG. 5 as measured by x-ray powder diffraction using an x-ray wavelength of 1.54 Å.

Provided herein as Embodiment 83 is the compound of any one of Embodiments 80-82, wherein the compound is characterized by a differential scanning calorimetry thermogram comprising an endotherm with an onset of about 144° C.

Provided herein as Embodiment 84 is the compound of any one of Embodiments 80-83, wherein the compound is characterized by a thermogravimetric analysis thermogram comprising a weight loss of about 1.5% when heated from about 25° C. to about 275° C.

Provided herein as Embodiment 85 is the compound of any one of Embodiments 80-84, wherein the compound is characterized by ¹⁹F solid state NMR comprising peaks at approximately -86, -96, -116, -127, -146, and -156 ppm.

Provided herein as Embodiment 86 is the compound of any one of Embodiments 80-85, wherein the compound is characterized by ¹⁹F solid state NMR substantially as depicted in FIG. 4.

Provided herein as Embodiment 87 is the compound of any one of Embodiments 80-86, wherein the compound is substantially pure.

Provided herein as Embodiment 88 is a pharmaceutical composition comprising the compound of any one of Embodiments 80-87 and a pharmaceutically acceptable excipient.

Provided herein as Embodiment 89 is a pharmaceutical composition comprising (1) the compound of any one of Embodiments 4-18, (2) the compound of any one of Embodiments 43-54, (3) the compound of any one of Embodiments 57-64, (4) the compound of any one of Embodiments 67-75, or (5) the compound of any one of Embodiments 80-86, or any mixtures thereof, and a pharmaceutically acceptable excipient.

Crystallization Techniques

Anti-Solvent Precipitation

Solutions of the compounds of the disclosure were prepared in various solvents and an anti-solvent was then added. The solids that formed were isolated and analyzed.

Alternatively, solutions of the compounds of the disclosure were prepared in various solvents, an anti-solvent was then added and the samples were allowed to evaporate. The solids that formed were isolated and analyzed.

Alternatively, solutions of the compounds of the disclosure were prepared in various solvents, an anti-solvent was then added and the samples were cooled to 2° C. to 8° C. The solids that formed were isolated and analyzed.

Sonication

Solutions or suspensions of the compounds of the disclosure were prepared in various solvents and sonicated in an ice bath for 90-180 minutes. The solids were isolated and analyzed.

Slow Cool

Saturated solutions of the compounds of the disclosure were prepared in various solvents at either ambient or elevated temperature. Samples prepared at elevated tem-

perature were allowed to cool to ambient or 2-8° C. The solids that formed were isolated and analyzed.

Evaporation

Solutions of the compounds of the disclosure were prepared in various solvents. Once complete dissolution was observed, the solvent was evaporated by vacuum at ambient or heated temperatures. The solids that formed were isolated and analyzed.

Slow Evaporation

Solutions of the compounds of the disclosure were prepared in various solvents. Once complete dissolution was observed, the solution was allowed to evaporate at ambient in a partially covered vial, with or without a blanket of nitrogen gas. The solids that formed were isolated and analyzed.

Alternatively, solutions of the compounds of the disclosure were prepared followed by sonication for about 90 minutes. Following sonication the samples were allowed to evaporate. Experiments that yielded glasses, were reworked by slurring the materials with a 15 fold addition of anti-solvent (hexane at 50° C. or water at room temperature). Any resulting solids were isolated and analyzed.

Stress Experiments

Solutions or suspensions of the compounds of the disclosure were prepared in various solvents followed by sonication for 60 minutes. Samples were then stirred to 30° C. for 24-72 hours, followed by stirring at 50° C. for 24 hours. Samples were analyzed by XRPD at each stage before final isolation and analysis.

Slurry Experiments

Solutions of the compounds of the disclosure were prepared by adding enough solids to a given solvent so that excess solids were present. All forms described below can be obtained from various solvents, including, but not limited, to the specific solvents described in the Examples. The mixture was then agitated in a sealed vial at either ambient or elevated temperature. After a given amount of time, the solids were isolated by vacuum or centrifuge filtration and analyzed.

Analytical Techniques

X-Ray Powder Diffraction (XRPD)

X-ray powder diffraction data was obtained using the Phillips X-ray automated powder diffractometer (X'Pert) that was equipped with a fixed slit and a real time multi strip (RTMS) detector. The radiation was CuK α (1.54 Å) and the voltage and current were 45 kV and 40 mA, respectively. Data were collected at room temperature from 3.0 to 40.0 degree 2-theta; step size was 0.0167 degrees; counting time was 15.240 seconds. The stage was rotated at a revolution time of 1.0 second.

Alternatively, X-ray powder diffraction data was obtained using the PANalytical Empyrean automated powder diffractometer that was equipped with a soller slit, beam stop, short antiscatter extension, antiscatter knife edge and a scanning position-sensitive detector (X'Celerator). The radiation was

CuK α (1.54 Å). A specimen of the sample was sandwiched between 3 um thick films and analyzed in transmission geometry.

Alternatively, X-ray powder diffraction data was obtained using the PANalytical X'Pert PRO X-ray diffraction system that was equipped with a programmable divergence slit and a real time multi strip (RTMS) detector. The radiation was CuK α (1.54 Å) and the voltage and current were 45 kV and 40 mA, respectively. Data were collected at room temperature from 3.0 to 30.0 or 5 to 45 degrees 2-theta; step size was 0.0334 degrees. The stage was rotated at a revolution time of 2.0 seconds.

It is noted that peak shift of about +/-0.2 degrees can occur in XRPD patterns and could be caused by factors such as sample preparation and instrument alignment.

Thermogravimetric Analysis (TGA)

Thermogravimetric analysis was performed on a TGA Discovery Series, TA Instruments. Samples were analyzed under nitrogen at heating rates of 10° C./min over a temperature range from 25° C. to 325° C.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry data was collected using standard DSC mode (Discovery Series, TA Instruments). A heating rate of 10° C./min was employed over a temperature range from 25° C. to 350° C. Analysis was run under nitrogen and samples were loaded in aluminum pans. Indium was used as a calibration standard.

Solid State NMR

Approximately 100 mg of sample was packed into a 4 mm ceramic rotor using the SSNMR packing tool. SSNMR spectra were acquired on a Bruker Avance III 500 MHz WB spectrometer. ¹⁹F spectra were collected using a Bruker double resonance MAS probe operating at a ¹H resonance frequency of 500 MHz. A 4-mm H/F/X spinning probe operating at a spinning frequency of 14 kHz was used for all experiments. For ¹⁹F measurement, a 4 us pi/2 pulse was used and ¹H decoupling was carried out using a spinal 64 sequence. A recycle delay of 1.26*T1 was used for optimal S/N/time.

EXAMPLES

Example 1: Identification of Solid State Forms of Compound 1

Within the pharmaceutical research and development field, the investigation of a suitable solid-state form represents a crucial step. Investigating a solid-state form comprises several decisions, mainly the investigation of an anhydrous, salt or co-crystal form and the investigation of a polymorph of the respective anhydrous, salt or co-crystal. During a lead optimization program, several properties of research compounds are optimized, typically leading to one or a few candidates that continue into exploratory development programs. Typically, in the assessment and optimization of physical chemical parameters during lead optimization, the main focus is on solubility. In the present case, Compound 1 has good solubility features. Beyond the optimization of solubility, further physical chemical parameters, such as (1) melting point, (2) thermal behavior, (3) hygroscopicity, (4) crystal habit, (5) polymorphic behavior or

physical stability, (6) impurity profile, and (7) chemical stability of the anhydrous or salt form, must be borne in mind when investigating the salt. The melting point of a drug, either as a free base, acid or salt form, should be higher than a certain threshold to allow processing steps such as drying or tableting. The assessment of thermal behavior, which is typically done by thermogravimetry (TGA) and differential scanning calorimetry (DSC), also includes solid-solid phase transitions. These may be either enantiotropic or monotropic and can be related to the conversion of one polymorph to another or one pseudo-polymorph to another pseudo-polymorph—e.g. a lower solvate or hydrate—or a true polymorph. Hygroscopicity plays a key role in the evaluation of solid-state forms, as this property is highly relevant for many process steps such as drying, storage, blending, granulation, to name but a few. Hygroscopicity can be investigated by dynamic vapor sorption (DVS). Basically, this technique yields information on the amount of moisture that is taken up by the compound at a certain relative humidity level. Discussing thermal behavior and hygroscopicity represents the link to another parameter that has to be considered in anhydrous or salt investigation: a manageable polymorphic behavior is required for an anhydrous or salt form to continue in pharmaceutical development. Therefore, at least a brief assessment of polymorphism is typically carried out in an anhydrous or salt-investigation procedure. In this sense, a manageable polymorphic behavior is not equivalent to the existence of only one or two polymorphic forms, but rather to render a situation where the conversion of polymorphic forms that are not equivalent. Crystal habits can influence anhydrous or salt investigations, and optimization in many cases means moving away a drug in the form of needle-shaped crystals towards e.g. platelets or even cubic crystals exhibiting better flowability. Salt investigation can be a tool to improve impurity profiles of drugs since pharmaceutical salts often exhibit crystal structures that are quite different from the structure of the corresponding free base or acid.

Polymorph and Salt Screen

Accordingly, a polymorph and salt screen of Compound 1 was conducted. Crystalline chloride, phosphate, and mesylate salts as well as crystalline anhydrate, hydrate and solvate forms were identified. None of the identified salts displayed particularly advantageous thermal properties based on DSC data or appeared of lower crystallinity. Of the several remaining free base polymorphs, including the hydrate and solvates, the crystalline anhydrous Form I showed surprising and unexpected advantages.

First, the crystalline anhydrous Form I of Compound 1 is the most thermodynamically stable polymorph identified in the screening process. The crystalline anhydrous Form II and III described herein below convert to crystalline anhydrous Form I upon heating or slurrying.

Specifically, crystalline anhydrous Form II converts to crystalline anhydrous Form I upon heating and recrystallization at 193° C. Crystalline anhydrous Form II converts to crystalline anhydrous Form I upon slurrying in water at 90° C. for 1 hour. A mixture of crystalline anhydrous Form I and crystalline anhydrous Form II converts to crystalline anhydrous Form I upon slurrying in 90/10 v/v water/acetonitrile at RT for 7 days. A mixture of crystalline anhydrous Form I and crystalline anhydrous Form II converts to crystalline anhydrous Form I upon slurrying in heptane at 80° C. for 1 day.

Crystalline anhydrous Form III melts at 180° C. Crystalline anhydrous Form III converts to crystalline anhydrous Form I upon melting and recrystallization at 220° C. A mixture of crystalline anhydrous Form I and crystalline anhydrous Form III converts to crystalline anhydrous Form I upon slurrying in ethanol at RT for 10 days. A mixture of crystalline anhydrous Form I and crystalline anhydrous Form III converts to crystalline anhydrous Form I upon slurrying in methanol at RT for 10 days.

The high melting point of crystalline anhydrous Form I is a further indicator of its thermodynamic stability (DSC endotherm onset of about 293° C.).

Second, crystalline anhydrous Form I is less hygroscopic compared to crystalline anhydrous Forms II and III (Form I absorbed 0.5-1.0% wt moisture between 0 and 90% RH at 25° C.; Form II absorbed 2-2.5% wt moisture between 0 and 90% RH at 25° C.; Form III absorbed 7.0% wt moisture between 0-95% RH at 25° C.).

Moreover, crystalline anhydrous Form I was physically and chemically stable in the solid state, showing no degradation peaks by HPLC or any changes in the investigated solid state properties, including XRPD, melting point onset and heat of fusion by DSC, and volatiles content by TGA, for 14 weeks at 25° C./60% RH, 40° C./75% RH, 40° C./ambient RH, and 60° C./ambient RH. Furthermore, crystalline anhydrous Form I was stable in an excipient compatibility study in 3 prototype blends that were stored for 4 weeks at 40° C./75% RH. Crystalline anhydrous Form I was also stable to ultraviolet and visible light in the solid state.

Accordingly, crystalline anhydrous Form I shows advantageous and unexpected overall properties, in particular when compared with other forms and salts identified.

Polymorph Screen

A polymorph screen to generate the different solid forms of the M atropisomer of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1) was carried out as described below. As a matter of convenience, “Compound 1” as referred to in the Examples that follow is to be understood to be the M atropisomer of Compound 1.

Example 1

Compound 1 can be made according to the procedure disclosed in US Publication 2018/0334454 published on Nov. 22, 2018, which is herein incorporated by reference in its entirety.

Amorphous Form I of Compound 1 was prepared by rotary evaporation from MeOH with secondary drying under vacuum at RT.

The relative peak areas of the amorphous form of the XRPD, TGA, DSC and ¹⁹F SSNMR are represented in FIGS. 1, 2, 3 and 4.

Differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 144° C.

Thermogravimetric analysis (TGA) thermogram comprising a weight loss of about 1.5% when heated from about 25° C. to about 275° C.

¹⁹F SSNMR: -86, -96, -116, -127, -146 and -156 ppm.

A number of anhydrous and hydrate forms of Compound 1 were investigated (see Table 1 below). Further characterization of these crystalline forms, such as melting point, thermal behavior, hygroscopicity, crystal habit, particle size, polymorphic behavior, stability, and purity, were investi-

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gated. These forms were characterized by methods including XRPD, TGA, and DSC analysis. Rel. Int % is the percent relative intensity based on the largest peak.

FIG. 21 illustrates the overlay of crystalline anhydrous Forms I, II, III and the variable hydrate Form I of Compound 1 (Forms I-III and variable hydrate Form I are in order from top to bottom).

TABLE 1

XRPD Differentiating Peaks						
Free Base Form	Peaks Unique to Each Form (KA1°)					
Form I	9.0	12.0	12.6	19.0	—	—
Form II	7.3	9.8	10.1	11.3	13.3	17.2
Form III	6.3	8.4	9.5	16.0	—	—
Hydrate Form I	6.9	8.0	9.6	12.4	13.1	—

Example 2: Preparation of Crystalline Anhydrous Form I of Compound 1

Crystalline anhydrous Form I was prepared by charging 1.5 g of crystalline anhydrous Form II of Compound 1 with 10 mL of water to form a slurry. The slurry was heated to 90° C. for 2 h, then stirred overnight at RT. The solids were filtered, dried under vacuum and identified as crystalline anhydrous Form I by XRPD. DSC endotherm onset of about 292.6° C., TGA comprising a weight loss of about 0.2% when heated from about 25° C. to about 275° C.

The crystalline anhydrous Form I prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 5), DSC (FIG. 6), TGA (FIG. 7), carbon 13 SSNMR (FIG. 8), and ¹⁹F SSNMR (FIG. 9).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.93 (d, J=6.84 Hz, 3H) 1.07 (d, J=6.63 Hz, 3H) 1.35 (d, J=6.84 Hz, 3H) 1.90 (s, 3H) 2.66-2.75 (m, 1H) 3.14 (br t, J=11.20 Hz, 1H) 3.59-3.75 (m, 2H) 3.97-4.08 (m, 1H) 4.08-4.22 (m, 1H) 4.22-4.43 (m, 2H) 4.90 (br s, 1H) 5.74-5.79 (m, 1H) 6.21 (br d, J=17.00 Hz, 1H) 6.65-6.75 (m, 2H) 6.79-6.92 (m, 1H) 7.18 (d, J=4.98 Hz, 1H) 7.23-7.31 (m, 1H) 8.22-8.33 (m, 1H) 8.38 (d, J=4.77 Hz, 1H) 10.19 (s, 1H)

¹³C SSNMR: 12, 13, 16, 21, 23, 31, 33, 38, 42, 44, 47, 50, 54, 107, 110, 111, 123, 124, 127, 128, 132, 145, 146, 150, 154, 156, 158, 160, 162, 166, 167.7 and 168 ppm.

¹⁹F SSNMR: -49, -60, -79, -90, -109, -120, -138, -150, -168 and -179 ppm.

TABLE 2

XRPD data of the crystalline anhydrous Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
8.8	72.02
9.0	32.38
10.8	89.48
12.0	17.57
12.6	5.21
12.8	7.83
13.6	70.38
13.9	8.16
14.2	64.52
14.3	15.98
15.0	54.34
15.4	34.78
15.5	11.84

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TABLE 2-continued

XRPD data of the crystalline anhydrous Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
17.4	10.60
17.6	11.10
18.0	22.28
18.6	20.76
18.7	41.59
19.0	100.00
19.2	13.83
19.9	34.21
20.0	20.81
20.2	2.92
20.9	8.05
21.2	2.59
21.7	14.40
22.0	9.77
22.2	16.27
22.5	18.45
22.9	21.27
23.1	14.15
23.7	15.87
23.9	10.39
25.0	19.32
25.3	4.26
25.6	1.90
25.8	6.05
26.1	7.93
26.3	4.28
26.6	12.27
26.8	8.19
27.3	7.42
27.8	3.31
28.0	11.20
28.5	3.83
28.8	8.53
29.1	2.01
29.4	13.68
29.7	9.66
30.2	13.60
30.9	1.84
31.3	1.53
31.5	5.71
31.7	3.54
31.9	1.13
32.3	1.55
32.6	1.69
32.8	2.47
33.0	2.11
33.6	3.23
33.9	5.14
34.2	3.90
34.7	0.67
34.9	1.76
35.0	1.62
35.4	1.10
35.8	2.43
36.5	0.59
37.0	4.04
37.0	2.30
37.3	0.80
37.7	0.66
38.0	1.27
38.3	2.60
38.4	4.02
39.1	0.51
39.4	1.88
39.8	0.90

Example 3: Preparation of the Anhydrous Form II of the Compound 1

The crystalline anhydrous Form II of Compound 1 was prepared by charging 0.987 g of amorphous Compound 1

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with 15 mL MeOH to produce a slurry. The isolated solids were identified as crystalline anhydrous Form II by XRPD.

DSC onset of about 192.5° C., TGA comprising a weight loss of about 1% to about 1.8% when heated from about 25° C. to about 250° C.

The crystalline anhydrous Form II of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 10), DSC (FIG. 11), TGA (FIG. 12), carbon 13 SSNMR (FIG. 13), and ¹⁹F SSNMR (FIG. 14).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.93 (d, J=6.63 Hz, 4H) 1.07 (d, J=6.84 Hz, 4H) 1.35 (d, J=6.63 Hz, 4H) 1.90 (s, 3H) 2.60-2.76 (m, 1H) 3.11-3.28 (m, 2H) 3.68 (br d, J=13.89 Hz, 2H) 4.08 (d, J=5.18 Hz, 2H) 4.32 (br d, J=13.68 Hz, 2H) 4.90 (br s, 1H) 5.74-5.79 (m, 1H) 6.21 (br d, J=16.17 Hz, 1H) 6.65-6.76 (m, 2H) 6.80-6.92 (m, 1H) 7.18 (d, J=4.98 Hz, 1H) 7.23-7.31 (m, 1H) 8.29 (br d, J=9.33 Hz, 1H) 8.38 (d, J=4.98 Hz, 1H) 10.19 (s, 1H).

¹³C SSNMR: 16, 18, 19, 20, 23, 25, 31, 32, 38, 40, 43, 46, 51, 57, 105, 107, 110, 117, 120, 123, 124, 125, 128, 132, 149, 152, 155, 158, 159, 163 and 166 ppm.

¹⁹F SSNMR: -59, -62, -89, -92, -119, -122, -148, -151, -179 and -181 ppm.

TABLE 3

XRPD data of the crystalline anhydrous Form II of Compound 1	
Pos. [° 2 Th.]	Rel. Int. [%]
7.3	55.69
9.8	22.74
10.1	13.34
10.4	26.87
11.3	100.00
11.5	38.51
11.9	17.55
13.3	19.19
14.3	37.78
14.7	63.63
14.9	20.80
15.8	1.24
17.2	47.51
18.1	9.48
18.4	37.17
18.6	6.86
19.2	31.06
19.8	5.10
20.4	11.69
20.9	10.16
21.1	10.57
21.4	3.78
21.7	3.26
22.1	18.04
22.4	12.23
22.6	4.78
23.1	20.56
23.8	9.50
24.3	17.04
24.7	3.75
25.6	6.63
26.2	6.15
27.1	9.80
27.3	12.94
27.9	2.58
28.3	6.04
28.5	7.17
28.9	7.06
29.4	4.82
29.6	6.76
30.7	4.35
31.2	4.41
31.5	1.70
31.9	0.83
32.6	2.54

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TABLE 3-continued

XRPD data of the crystalline anhydrous Form II of Compound 1	
Pos. [° 2 Th.]	Rel. Int. [%]
33.3	1.23
34.0	0.53
34.6	1.58
35.0	1.66
35.4	2.35
36.2	2.20
36.8	1.47
37.2	1.73
38.0	2.55
38.4	4.75
38.8	2.68

Example 4: Preparation of Crystalline Anhydrous Form III of Compound 1

The crystalline anhydrous Form III of Compound 1 was prepared by drying the acetone solvate Form I of Compound 1 by vacuum at ~65-76° C. DSC endotherm onset of about 194° C., TGA comprising an approximate negligible weight loss when heated from about 25° C. to about 250° C.

The crystalline anhydrous Form III of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 15), DSC (FIG. 16), and TGA (FIG. 17).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.93 (d, J=6.82 Hz, 3H) 1.07 (d, J=6.61 Hz, 3H) 1.35 (d, J=6.61 Hz, 2H) 1.90 (s, 2H) 2.64-2.80 (m, 1H) 3.14 (br t, J=10.66 Hz, 1H) 3.45-3.57 (m, 1H) 3.58-3.76 (m, 1H) 3.94-4.08 (m, 1H) 4.14 (br d, J=13.00 Hz, 1H) 4.21-4.47 (m, 2H) 4.90 (br s, 1H) 5.76 (dd, J=10.44, 2.13 Hz, 1H) 6.21 (br d, J=16.84 Hz, 1H) 6.55-6.78 (m, 2H) 6.86 (dt, J=16.20, 11.29 Hz, 1H) 7.13-7.21 (m, 1H) 7.21-7.33 (m, 1H) 8.21-8.34 (m, 1H) 8.39 (d, J=4.90 Hz, 1H) 10.20 (br s, 1H).

TABLE 4

XRPD data of the Anhydrous Form III of Compound 1	
Pos. [° 2 Th.]	Rel. Int. [%]
6.3	14.11
8.4	63.06
9.5	84.68
10.4	12.93
12.8	6.80
13.0	6.79
13.7	4.59
14.9	12.72
15.4	45.73
15.5	69.05
16.0	79.08
16.6	8.35
17.6	100.00
18.2	9.32
18.7	37.73
19.2	16.82
20.0	36.44
20.6	13.07
20.8	9.52
21.7	3.50
21.7	16.74
22.7	5.52
23.0	13.50
23.2	4.81
24.2	11.39
24.9	3.83

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TABLE 4-continued

XRPD data of the Anhydrous Form III of Compound 1	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
25.4	10.81
25.9	5.35
26.7	17.58
26.8	5.18
27.2	10.38
27.5	12.87
27.9	4.42
28.3	7.66
28.6	15.70
29.3	3.10
29.7	1.70
30.2	1.02
31.4	2.93
32.2	3.52
32.5	3.97
33.1	2.31
33.7	1.35
34.6	4.91
35.5	3.74
35.8	2.54
36.7	1.18
37.3	1.65
38.0	2.18
39.0	1.57

Example 5: Preparation of Variable Hydrate Form I of Compound 1

The variable hydrate Form I of Compound 1 was prepared by dissolving Compound 1 in MeOH at RT, polish filtering then charging with aliquots of water as an antisolvent until precipitation occurred. Solids were isolated after stirring at RT for 13 days.

DSC first endotherm onset of about at 91° C., TGA comprising an approximate 11% weight loss when heated from about 39° C. to about 160° C. (3.9 mol water).

Karl Fischer 10.63% (3.7 mol) water.

The crystalline variable hydrate Form I prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 18), DSC (FIG. 19), and TGA (FIG. 20).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 (d, J=6.62 Hz, 3H) 1.08 (d, J=6.84 Hz, 3H) 1.35 (d, J=6.63 Hz, 3H) 1.90 (s, 3H) 2.61-2.79 (m, 1H) 3.15 (br t, J=11.01 Hz, 1H) 3.40-3.58 (m, 2H) 3.59-3.84 (m, 3H) 3.86-4.09 (m, 1H) 4.15 (br d, J=12.39 Hz, 1H) 4.21-4.47 (m, 3H) 4.90 (br s, 2H) 5.73-5.82 (m, 1H) 6.15-6.21 (m, 1H) 6.23 (br d, J=4.92 Hz, 1H) 6.63-6.77 (m, 3H) 6.78-7.03 (m, 2H) 7.14-7.31 (m, 3H) 8.14-8.35 (m, 1H) 8.39 (d, J=4.92 Hz, 1H).

TABLE 5

XRPD data of the Crystalline Variable Hydrate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
4.0	10.00
4.4	12.08
4.8	17.94
6.9	12.94
8.0	100.00
8.8	8.55
9.6	26.66
10.8	10.41
11.3	13.06

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TABLE 5-continued

XRPD data of the Crystalline Variable Hydrate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
12.4	36.89
13.0	43.60
13.1	41.65
14.2	5.04
14.6	35.20
14.9	38.07
15.2	40.25
15.7	7.44
16.2	40.04
16.4	17.22
16.6	29.36
17.3	54.43
17.4	68.45
17.9	16.60
18.1	30.16
18.6	5.51
19.3	27.13
19.5	35.91
19.8	13.20
20.4	8.31
20.8	20.25
21.0	21.40
21.5	43.72
22.8	14.71
23.0	13.61
23.6	14.15
24.1	28.65
24.6	20.05
25.1	28.24
25.3	31.05
25.8	35.64
26.4	35.12
26.7	28.61
27.8	31.13
28.7	25.99
29.2	25.20
30.6	14.61
31.5	19.08
32.2	8.81
32.7	8.36
36.7	2.96
37.2	4.34

Example 6: Preparation of Crystalline THF Solvate Form I of Compound 1

The crystalline THE solvate Form I of Compound 1 was prepared by placing amorphous Compound 1 in a small open vial then placing this vial inside a larger vial containing THE and capped to vapor stress the solids at RT for 4 days.

DSC endotherm onset of about 165° C., TGA comprising an approximate 13.4% weight loss when heated from about 130° C. to about 160° C. (1.2 mol THF)

NMR 1.1 mol THE The crystalline THE solvate Form I prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 22), DSC (FIG. 23), and TGA (FIG. 24).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.94 (d, J=6.62 Hz, 3H) 1.08 (d, J=6.62 Hz, 3H) 1.35 (d, J=6.62 Hz, 3H) 1.68-1.84 (m, 4H) 1.90 (s, 3H) 2.62-2.93 (m, 1H) 3.15 (br t, J=11.33 Hz, 1H) 3.49-3.75 (m, 10H) 3.87-4.09 (m, 1H) 4.09-4.21 (m, 1H) 4.22-4.47 (m, 4H) 4.91 (br s, 2H) 5.71-5.83 (m, 2H) 6.21 (br dd, J=16.88, 4.70 Hz, 1H) 6.64-6.78 (m, 3H) 6.78-6.99 (m, 1H) 7.14-7.22 (m, 1H) 7.28 (td, J=8.33, 7.05 Hz, 1H) 8.18-8.35 (m, 1H) 8.39 (d, J=4.92 Hz, 1H) 10.21 (br s, 1H)

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TABLE 6

XRPD data of the Crystalline THF solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
7.0	54.90
9.0	100.00
9.8	46.41
10.3	5.55
10.5	99.74
10.9	11.45
11.2	5.67
11.8	5.10
13.7	24.35
14.0	9.45
14.1	59.90
14.7	6.49
16.6	52.03
17.0	37.49
17.3	56.50
18.0	3.30
18.3	16.05
18.7	41.48
18.8	54.81
19.1	31.94
19.4	8.97
19.7	25.38
20.0	4.56
20.4	7.31
20.6	11.11
20.8	6.26
21.1	22.76
21.2	34.92
22.1	5.75
22.3	18.70
22.5	33.36
22.8	36.37
23.0	10.85
23.2	2.20
23.6	3.63
24.0	9.03
24.4	9.86
24.7	3.54
24.8	3.71
25.2	32.94
25.6	20.13
25.8	21.45
26.0	7.67
26.6	8.01
26.9	1.62
27.3	2.20
27.5	7.64
27.6	9.42
28.1	1.43
28.4	13.20
28.7	3.64
28.9	5.81
29.2	5.97
29.5	2.80
29.8	3.78
30.0	4.57
30.2	5.86
30.6	3.73
31.1	1.64
31.6	3.62
31.9	1.07
32.5	1.55
33.1	5.45
33.3	1.71
33.7	0.66
34.1	2.01
34.3	2.49
35.4	1.19
35.7	1.20
36.2	4.29
36.3	4.30
36.5	2.51
36.9	1.70
37.1	1.30

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TABLE 6-continued

XRPD data of the Crystalline THF solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
37.5	2.10
38.0	1.09
38.2	1.05
38.9	3.39
39.4	1.73

Example 7: Preparation of Crystalline MeCN
Solvate Form I of Compound 1

The crystalline MeCN solvate Form I was prepared by slurry of compound 1 in MeCN at RT for 14 days.

DSC endotherm onset of about 112 $^{\circ}$ C., TGA comprising an approximate 6.9% weight loss when heated from about 38 $^{\circ}$ C. to about 170 $^{\circ}$ C. (1 mol MeCN).

NMR 0.9 mol MeCN.

The crystalline MeCN solvate Form I prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 25), DSC (FIG. 26), and TGA (FIG. 27).

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.85-1.00 (m, 3H) 1.07 (d, J=6.82 Hz, 3H) 1.35 (d, J=6.82 Hz, 3H) 1.90 (s, 3H) 1.99-2.16 (m, 2H) 2.52-2.78 (m, 1H) 3.14 (br s, 1H) 3.35-3.56 (m, 1H) 3.57-3.84 (m, 2H) 3.86-4.09 (m, 1H) 4.09-4.19 (m, 1H) 4.19-4.47 (m, 2H) 4.90 (br s, 1H) 5.66-5.80 (m, 1H) 6.20 (br dd, J=16.73, 4.58 Hz, 1H) 6.61-6.76 (m, 2H) 6.78-6.94 (m, 1H) 7.11-7.21 (m, 1H) 7.21-7.31 (m, 1H) 8.16-8.36 (m, 2H) 8.39 (d, J=4.69 Hz, 1H) 10.21 (br s, 1H).

TABLE 7

XRPD data of the Crystalline MeCN solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
7.2	72.45
9.9	52.43
10.0	37.15
10.2	8.87
10.5	2.74
11.2	91.77
11.3	15.89
11.6	8.89
13.2	4.06
13.7	3.17
14.2	25.71
14.5	100.00
15.7	1.02
16.6	15.62
16.9	66.32
17.2	2.44
17.4	4.61
18.0	14.01
18.2	53.02
18.7	56.63
18.9	49.31
19.8	3.70
20.1	21.31
20.4	16.05
20.8	4.63
21.0	5.42
21.7	73.71
22.3	5.02
22.5	5.69
22.7	34.41
23.0	6.77

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TABLE 7-continued

XRPD data of the Crystalline MeCN solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
23.4	15.57
23.6	15.11
24.1	37.36
25.0	8.92
25.3	10.74
25.7	13.79
26.5	21.93
26.8	9.15
27.0	26.55
27.4	8.80
27.5	12.09
28.0	11.68
28.4	12.41
28.6	11.67
28.8	8.71
29.1	10.79
29.7	3.00
30.1	3.21
30.5	13.17
30.8	5.66
31.0	9.44
31.2	3.79
31.9	1.38
32.2	5.20
32.3	7.29
33.5	2.46
34.0	1.40
34.4	2.91
34.9	3.17
35.2	3.57
35.4	2.40
36.2	0.94
36.6	2.12
37.0	4.21
37.7	3.05
37.9	5.41
38.0	3.75
38.5	2.87
38.9	3.18

Example 8: Preparation of Crystalline MEK
Solvate Form I of Compound 1

The crystalline MEK solvate Form I was prepared by dissolving Compound 1 in MEK at RT, polish filtering then charging with aliquots of heptane as an antisolvent until precipitation occurred. Solids were isolated after stirring at RT for 13 days. Also prepared by slurry of amorphous Compound 1 in MEK at RT.

DSC endotherm onset of about 106° C., TGA comprising an approximate 10.7% weight loss when heated from about 39° C. to about 197° C. (0.9 mol MEK)

NMR 0.8 mol MEK.

The crystalline MEK solvate Form I prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 28), DSC (FIG. 29), and TGA (FIG. 30).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.92 (q, J=7.05 Hz, 5H) 1.08 (d, J=6.62 Hz, 3H) 1.35 (d, J=6.62 Hz, 3H) 1.90 (s, 3H) 2.04-2.10 (m, 2H) 2.36-2.49 (m, 2H) 2.60-2.93 (m, 1H) 3.15 (br s, 1H) 3.36-3.57 (m, 2H) 3.57-3.84 (m, 4H) 3.86-4.09 (m, 2H) 4.15 (br d, J=12.82 Hz, 1H) 4.22-4.46 (m, 4H) 4.91 (br s, 2H) 5.72-5.83 (m, 2H) 6.00-6.21 (m, 1H) 6.23 (br d, J=4.49 Hz, 1H) 6.64-6.78 (m, 3H) 6.78-7.00 (m, 2H) 7.17-7.31 (m, 3H) 8.16-8.35 (m, 1H) 8.39 (d, J=4.92 Hz, 1H) 10.22 (br s, 1H).

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TABLE 8

XRPD data of the Crystalline MEK solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
7.0	47.52
8.8	70.25
9.8	56.17
10.4	100.00
10.9	22.80
11.2	11.60
11.8	9.64
13.6	31.04
14.1	78.89
14.7	19.18
16.6	79.53
16.8	30.39
17.0	26.79
17.2	47.48
17.5	3.12
18.1	5.01
18.4	23.39
18.7	35.48
18.9	65.12
19.2	48.49
19.4	10.83
19.7	46.72
20.4	6.72
20.7	15.78
20.9	6.30
21.2	80.14
22.1	8.83
22.4	32.98
22.6	48.82
22.7	34.64
22.9	13.33
23.7	9.34
24.1	18.80
24.5	27.07
24.8	11.35
25.0	28.12
25.3	17.14
25.7	36.16
25.8	25.93
26.3	8.43
26.8	6.92
27.0	2.12
27.2	3.88
27.4	8.69
27.6	7.15
27.9	1.14
28.2	6.71
28.3	13.70
28.6	8.63
29.0	18.29
29.6	7.09
30.1	14.00
30.3	2.13
30.7	3.85
31.3	3.80
31.71	4.92
32.0	0.54
32.5	0.62
32.8	4.00
33.2	2.69
33.5	5.80
34.1	5.30
34.7	1.61
35.0	0.76
35.5	2.20
36.0	5.55
36.2	7.66
36.6	1.43
37.0	0.51
37.5	3.76
38.1	1.54
38.4	1.60
38.7	2.93
39.3	0.73

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TABLE 8-continued

XRPD data of the Crystalline MEK solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ Th.]	Rel. Int. [%]
39.6	4.20

Example 9: Preparation of the Crystalline EtOAc
Solvate Form I of Compound 1

The crystalline EtOAc Solvate Form I was prepared by a
slurry of Compound 1 with ethyl acetate (EtOAc) at RT for
24 h.

The crystalline MEK solvate Form I prepared above was
characterized by proton NM/R and X-ray powder diffraction
(XRPD) data (FIG. 31)

TABLE 9

XRPD data of crystalline EtOAc Solvate Form I of Compound 1: XRPD Peak Table:	
Pos. [$^{\circ}$ Th.]	Rel. Int. [%]
7.1	8.9
9.0	55.8
9.8	36.0
10.5	100.0
11.0	19.6
11.3	5.6
11.9	1.9
12.5	2.2
13.7	21.3
14.2	48.6
14.7	11.8
16.7	51.6
17.0	39.5
17.4	40.6
18.1	4.6
18.3	10.5
18.9	38.1
19.2	23.2
19.5	11.8
19.7	30.5
20.0	2.9
20.4	3.8
20.7	12.9
21.3	59.1
22.1	3.7
22.6	30.7
22.8	34.2
23.1	14.8
23.8	9.9
24.1	8.2
24.5	19.9
24.8	11.5
25.1	35.4
25.4	11.8
25.8	35.3
26.0	24.8
26.6	17.1
27.0	2.0
27.5	9.1
27.7	4.7
28.0	4.2
28.6	13.0
29.0	10.6
29.2	10.9
29.7	5.0
30.2	4.8
30.9	5.5
31.3	3.2

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TABLE 9-continued

XRPD data of crystalline EtOAc Solvate Form I of Compound 1: XRPD Peak Table:	
Pos. [$^{\circ}$ Th.]	Rel. Int. [%]
31.7	4.5
32.1	3.4
32.6	1.8
33.1	6.8
33.6	5.2
34.0	2.9
34.3	4.0
34.8	1.2
35.4	2.4
35.7	1.8
35.9	3.9
36.3	10.9
36.8	2.9
37.0	2.7
37.3	1.9
37.9	2.7
38.1	3.0
39.1	4.3
39.7	3.3
40.1	3.1
40.4	3.6
41.2	2.5
41.6	3.6
42.0	1.3
42.5	2.2
43.2	4.1
43.5	3.4
43.8	2.2
44.1	2.6
44.4	2.3

Example 10: Preparation of the DMF Solvate Form
I of Compound 1

The crystalline DMF solvate Form I of Compound 1 was
prepared by a slurry of Compound 1 in DMF/water at RT for
24 h.

The crystalline DMF solvate Form I of Compound 1
prepared above was characterized by proton NMR, X-ray
powder diffraction (XRPD) data (FIG. 32), DSC (FIG. 33),
and TGA (FIG. 34).

DSC endotherm onset of about 74 $^{\circ}$ C., TGA comprising
an approximate 17% weight loss when heated from about
36 $^{\circ}$ C. to about 195 $^{\circ}$ C.

NMR 1-2 mol DMF.

^1H NMR (500 MHz, DMSO- d_6) δ ppm 0.94 (d, J=6.49
Hz, 4H) 1.08 (d, J=6.75 Hz, 4H) 1.35 (d, J=6.75 Hz, 4H)
1.91 (s, 4H) 2.30 (s, 1H) 2.55 (t, J=5.58 Hz, 1H) 2.73 (s, 6H)
2.89 (s, 5H) 3.00-3.21 (m, 1H) 3.27 (br d, J=13.49 Hz, 2H)
3.34 (br s, 5H) 3.60-3.74 (m, 2H) 3.96-4.16 (m, 1H) 4.32 (br
d, J=13.75 Hz, 2H) 4.39 (br s, 1H) 4.90 (br s, 1H) 5.67-5.86
(m, 1H) 6.20 (br dd, J=16.61, 7.27 Hz, 1H) 6.64-6.77 (m,
2H) 6.79-6.92 (m, 1H) 7.17-7.32 (m, 2H) 7.95 (s, 1H) 8.28
(br dd, J=16.22, 9.21 Hz, 1H) 8.40 (d, J=4.93 Hz, 1H) 10.19
(d, J=1.30 Hz, 1H).

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TABLE 10

XRPD data of the Crystalline DMF Solvate Form I of Compound 1 XRPD Peak Table:		
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]	
7.8	100.0	
8.1	60.0	
9.0	19.1	
12.4	17.5	5
13.3	7.5	
14.4	25.9	10
15.0	7.4	
16.1	11.4	
16.8	26.5	
17.3	17.5	
18.9	12.3	15
19.9	58.6	
20.8	38.6	
21.8	11.0	
23.3	17.0	
24.3	12.6	
24.9	11.5	20
25.4	12.7	
26.8	17.8	
27.3	11.1	
28.3	30.4	
28.6	38.6	
29.4	12.3	25
30.4	6.0	
31.6	6.2	
34.0	3.3	
35.7	1.9	
37.9	2.6	
42.2	2.2	30

Example 11: Preparation of the Crystalline DCM
Solvate Form I of Compound 1

The crystalline DCM solvate Form I of Compound 1 was prepared by dissolving Compound 1 in DCM at RT, polish filtering, then charging the aliquots of heptane as an anti-solvent until precipitation occurred. Solids were isolated after stirring at RT for 1 h.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.84-1.02 (m, 2H) 1.07 (d, J=6.61 Hz, 2H) 1.35 (d, J=6.82 Hz, 2H) 1.90 (s, 2H) 2.64-2.80 (m, 1H) 3.14 (br t, J=11.19 Hz, 1H) 3.45-3.57 (m, 1H) 3.58-3.84 (m, 2H) 3.86-4.09 (m, 1H) 4.09-4.21 (m, 1H) 4.21-4.46 (m, 2H) 4.90 (br s, 1H) 5.65-5.86 (m, 2H) 6.08-6.28 (m, 1H) 6.63-6.76 (m, 2H) 6.86 (dt, J=16.46, 11.27 Hz, 1H) 7.12-7.21 (m, 1H) 7.21-7.31 (m, 1H) 8.16-8.36 (m, 2H) 8.39 (d, J=4.90 Hz, 1H) 10.20 (br s, 1H).

The crystalline DCM solvate Form I of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 35), DSC (FIG. 36), and TGA (FIG. 37).

DSC endotherm onset of about 174 $^{\circ}$ C., TGA comprising an approximate 7.2% weight loss when heated from about 40 $^{\circ}$ C. to about 200 $^{\circ}$ C. (0.5 mol DCM) from 40-200 $^{\circ}$.

NMR 0.5 mol DCM

TABLE 11

XRPD data of the Crystalline DCM Solvate Form I of Compound 1 XRPD Peak Table:		
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]	
7.1	53.6	
9.5	100.0	
10.1	64.3	

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TABLE 11-continued

XRPD data of the Crystalline DCM Solvate Form I of Compound 1 XRPD Peak Table:		
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]	
10.9	95.6	
11.7	9.1	
11.6	3.4	
13.8	12.2	
14.0	26.5	
14.3	95.5	
14.6	12.7	
15.2	7.2	
16.6	23.7	
16.8	97.7	
17.6	36.1	
17.8	86.9	
18.6	35.9	
18.9	65.9	
19.1	88.3	
19.8	6.0	
20.2	31.9	
20.7	16.3	
21.0	13.2	
21.3	16.8	
21.4	65.3	
21.8	33.6	
22.8	74.2	
23.2	12.1	
23.5	23.7	
23.6	43.1	
23.9	10.5	
24.4	11.9	
25.0	17.6	
25.2	12.8	
25.8	21.9	
26.2	58.2	
26.5	18.3	
26.7	19.1	
27.2	14.4	
27.3	13.4	
27.7	14.8	
28.0	14.5	
28.3	22.0	
28.7	12.6	
29.0	9.0	
29.3	9.3	
29.5	5.3	
29.9	6.6	
30.1	8.7	
30.4	17.3	
30.8	6.6	
31.3	3.7	
31.7	4.0	
32.3	7.2	
32.5	7.7	
33.0	2.4	
33.5	1.9	
34.2	8.3	
34.8	2.8	
35.7	2.3	
36.9	2.4	
37.3	6.5	
37.8	9.6	
38.8	2.4	
39.1	3.6	

Example 12: Preparation of the Crystalline Acetone
Solvate Form I of Compound 1

The crystalline acetone solvate Form I of Compound 1 was prepared by a slurry of amorphous Compound 1 in acetone/water (50:50) at RT or a slurry of Compound 1 in acetone/water (50:50) at 2-8 $^{\circ}$ C. for 15 days.

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The crystalline acetone solvate Form I of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 38), DSC (FIG. 39), and TGA (FIG. 40).

DSC endotherm onset of about 72° C., TGA comprising an approximate 21.4% weight loss when heated from about 38° C. to about 130° C. (0.7 mol acetone and 5.3 mol water).

NMR 0.7 mol acetone.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.84-1.00 (m, 3H) 1.07 (d, J=6.61 Hz, 3H) 1.34 (d, J=6.61 Hz, 3H) 1.90 (s, 3H) 2.05-2.12 (m, 3H) 2.52-2.78 (m, 2H) 3.08-3.21 (m, 1H) 3.45-3.57 (m, 1H) 3.67 (br d, J=11.72 Hz, 2H) 3.97-4.06 (m, 1H) 4.08-4.21 (m, 1H) 4.32 (br d, J=13.85 Hz, 2H) 4.90 (br s, 1H) 5.54-5.80 (m, 2H) 5.99-6.26 (m, 2H) 6.52-6.75 (m, 2H) 6.84 (br s, 1H) 7.09-7.30 (m, 2H) 8.12-8.36 (m, 3H) 8.38 (d, J=4.90 Hz, 1H) 10.21 (br s, 1H).

TABLE 12

XRPD data of the Crystalline Acetone Solvate Form I of Compound 1 XRPD Peak Table	
Pos. [°2 Th.]	Rel. Int. [%]
5.6	1.4
7.8	100.0
8.1	38.3
9.0	13.1
11.2	2.3
12.4	22.1
12.6	4.9
13.2	36.5
14.3	78.7
14.9	10.7
15.0	10.1
15.7	4.7
16.4	20.2
16.6	7.7
16.8	12.4
16.9	19.6
17.0	9.4
17.3	11.5
17.5	10.8
18.0	2.1
18.8	26.4
19.8	16.6
20.1	32.6
20.2	24.2
20.5	37.7
20.7	17.3
21.4	5.0
21.6	14.4
22.6	2.7
23.1	4.1
23.2	6.4
23.4	7.3
23.9	12.0
24.0	17.6
24.7	11.9
25.0	10.8
25.6	15.7
26.1	11.1
26.6	10.6
26.9	22.9
27.1	17.5
27.8	5.7
28.1	22.0
28.4	8.6
28.8	16.2
29.1	13.0
29.4	10.9
30.2	13.5
30.9	6.5
31.3	7.7
31.6	7.3
31.9	5.6
32.6	4.9

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TABLE 12-continued

XRPD data of the Crystalline Acetone Solvate Form I of Compound 1 XRPD Peak Table	
Pos. [°2 Th.]	Rel. Int. [%]
33.2	2.9
33.6	7.3
34.5	6.2
35.0	3.8
35.4	3.7
35.8	3.3
36.6	2.9
36.9	3.8
37.3	5.3
37.8	4.0
38.7	4.5
39.3	3.2

Example 13: Preparation of the Crystalline Acetone Solvate Form II of Compound 1

The crystalline acetone solvate Form II of Compound 1 was prepared by a slurry Compound 1 in acetone at 2-8° C. for 15 days.

The crystalline acetone solvate Form II of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 41), DSC (FIG. 42), and TGA (FIG. 43).

DSC endotherm onset of about 137° C., TGA comprising an approximate 7.3% weight loss when heated from about 100° C. to about 200° C. (0.8 mol acetone).

NMR 0.7 mol acetone

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.83-1.02 (m, 3H) 1.07 (d, J=6.82 Hz, 2H) 1.35 (d, J=6.61 Hz, 2H) 1.90 (s, 2H) 2.09 (s, 3H) 2.52-2.77 (m, 1H) 3.18 (br s, 1H) 3.45-3.57 (m, 1H) 3.66 (br s, 4H) 3.96-4.08 (m, 1H) 4.08-4.20 (m, 1H) 4.32 (br d, J=13.64 Hz, 3H) 4.90 (br s, 2H) 5.69-5.80 (m, 1H) 6.15-6.26 (m, 1H) 6.60-6.75 (m, 2H) 6.79-6.94 (m, 1H) 7.07-7.21 (m, 1H) 7.27 (td, J=8.31, 7.03 Hz, 1H) 8.20-8.36 (m, 2H) 8.39 (d, J=4.90 Hz, 1H) 10.20 (br s, 1H).

TABLE 13

XRPD data of the Crystalline Acetone Solvate Form II of Compound 1 XRPD Peak Table	
Pos. [°2 Th.]	Rel. Int. [%]
7.1	60.1
9.1	38.0
9.9	47.8
10.3	15.8
10.6	56.1
10.9	13.4
11.3	15.8
11.8	8.7
12.7	1.1
13.8	27.0
14.0	17.3
14.2	59.6
14.7	13.0
16.7	60.7
16.9	26.6
17.1	14.3
17.4	29.3
17.7	7.9
18.2	12.6
18.5	17.5
18.7	33.6
19.0	100.0

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TABLE 13-continued

XRPD data of the Crystalline Acetone Solvate Form II of Compound 1 XRPD Peak Table	
Pos. [° 2 Th.]	Rel. Int. [%]
19.6	4.7
19.9	32.0
20.3	3.3
20.8	29.1
21.3	46.3
22.3	37.3
22.7	50.5
23.0	32.6
23.7	5.9
24.1	16.5
24.6	17.2
24.9	5.0
25.3	18.9
25.5	17.5
25.8	29.5
26.1	13.0
26.8	4.9
27.0	12.0
27.3	4.9
27.8	13.6
28.2	9.8
28.6	12.5
28.8	5.9
29.2	11.7
29.5	4.8
29.7	5.9
29.9	3.7
30.3	7.0
30.7	7.2
30.7	4.2
31.4	5.2
31.7	6.6
32.0	4.5
33.1	2.9
33.3	7.6
34.3	4.9
35.4	0.8
35.7	2.3
36.2	1.7
36.5	6.2
37.0	2.4
37.4	1.0
37.7	2.8
37.9	4.2
38.6	2.1
39.1	2.8
39.7	3.8

Example 14: Preparation of the Crystalline
P-Dioxane Solvate Form I of Compound 1

The crystalline p-dioxane solvate Form I of Compound 1 was prepared by a slurry of Compound 1 in p-dioxane at RT for 14 days.

The crystalline p-dioxane solvate Form I of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 44), DSC (FIG. 45), and TGA (FIG. 46).

DSC endotherm onset of about 112° C., TGA comprising an approximate 23.2% weight loss when heated from about 25° C. to about 150° C. (1.9 mol p-dioxane)

NMR 1.9 mol p-dioxane

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.84-1.00 (m, 3H) 1.07 (d, J=6.61 Hz, 3H) 1.35 (d, J=6.82 Hz, 3H) 1.90 (s, 2H) 2.52-2.77 (m, 2H) 3.05-3.28 (m, 1H) 3.32 (s, 4H) 3.58-3.78 (m, 3H) 3.98-4.07 (m, 1H) 4.09-4.20 (m, 1H) 4.09-4.19 (m, 1H) 4.15-4.43 (m, 1H) 4.16-4.21 (m, 1H) 4.22-4.45 (m, 1H) 4.23-4.45 (m, 1H) 4.90 (br s, 1H) 5.61-5.80 (m, 1H) 6.20 (br

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dd, J=16.62, 4.48 Hz, 1H) 6.58-6.76 (m, 2H) 6.79-6.93 (m, 1H) 7.10-7.21 (m, 1H) 7.21-7.31 (m, 1H) 8.14-8.36 (m, 3H) 8.39 (d, J=4.90 Hz, 1H) 10.20 (br s, 1H)

TABLE 14

XRPD data of the Crystalline p-Dioxane Solvate Form I of Compound 1 XRPD Peak Table	
Pos. [° 2 Th.]	Rel. Int. [%]
7.8	94.7
9.5	83.9
9.6	55.6
10.2	7.1
11.0	59.4
11.3	30.2
11.8	1.0
12.9	71.9
13.2	1.6
13.7	6.4
14.3	13.0
15.8	81.2
16.4	4.8
16.6	4.5
17.7	81.5
18.1	49.0
18.3	40.0
18.6	85.4
18.8	100.0
19.0	63.4
19.2	94.1
19.8	88.2
20.0	73.8
20.4	13.1
20.5	42.2
20.9	13.0
21.2	41.5
21.6	22.5
21.7	20.6
22.0	34.7
22.4	6.1
22.7	8.0
23.0	3.2
23.3	14.6
23.6	32.9
23.7	47.2
24.1	55.3
24.3	8.5
25.0	25.5
25.9	21.9
26.6	26.6
27.0	20.1
27.3	7.1
27.4	9.2
27.7	10.6
28.0	6.4
28.1	5.0
28.6	20.8
28.8	6.5
29.1	6.3
29.2	5.9
29.6	6.6
30.0	7.1
30.4	4.6
30.5	8.0
31.0	12.2
31.5	3.3
32.0	8.6
32.3	5.4
32.7	1.2
33.3	9.4
34.3	3.1
34.9	4.0
35.5	4.3
35.9	5.3
36.3	1.1
36.8	2.8
37.0	5.2
37.4	1.0

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TABLE 14-continued

XRPD data of the Crystalline p-Dioxane Solvate Form I of Compound 1 XRPD Peak Table	
Pos. [° 2 Th.]	Rel. Int. [%]
37.8	1.7
38.9	3.1
39.5	3.6

Example 15: Preparation of the Crystalline
Methanol Solvate Form I of Compound 1

The crystalline methanol (MeOH) solvate Form I of Compound 1 was prepared by placing Compound 1 in a small open vial then placing this vial inside a larger vial containing MeOH and capped to vapor stress the solids at RT for 4 days.

The crystalline MeOH Solvate Form I of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 47), DSC (FIG. 48), and TGA (FIG. 49).

DSC endotherm onset of about 57° C., TGA comprising an approximate 5.2% weight loss when heated from about 38° C. to about 220° C. (1.0 mol MeOH)

NMR 0.8 mol MeOH

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.94 (d, J=6.62 Hz, 3H) 1.08 (d, J=6.62 Hz, 3H) 1.35 (d, J=6.84 Hz, 3H) 1.90 (s, 3H) 2.64-2.80 (m, 1H) 3.18 (d, J=4.92 Hz, 3H) 3.48-3.76 (m, 2H) 3.97-4.21 (m, 2H) 4.21-4.47 (m, 2H) 4.91 (br s, 1H) 5.69-5.86 (m, 1H) 6.21 (br dd, J=16.67, 4.49 Hz, 1H) 6.63-6.79 (m, 2H) 6.80-6.98 (m, 1H) 7.17-7.31 (m, 2H) 8.18-8.35 (m, 1H) 8.39 (d, J=4.92 Hz, 1H) 10.22 (br s, 1H)

TABLE 15

XRPD data of the Crystalline MeOH Solvate Form I of Compound 1 XRPD Peak Table	
Pos. [° 2 Th.]	Rel. Int. [%]
7.2	22.9
9.0	30.8
9.7	42.7
10.3	13.3
10.6	100.0
11.2	44.1
12.1	4.1
13.7	26.4
14.1	10.9
14.4	91.4
14.9	43.3
16.0	0.9
16.8	91.1
17.0	18.4
17.2	5.0
17.4	37.0
17.6	15.5
17.8	22.7
18.1	8.0
18.7	35.3
18.9	4.5
19.1	3.6
19.5	74.7
20.0	1.7
20.3	1.6
20.6	4.7
21.1	21.9
21.3	2.9
21.7	68.4
22.0	5.9

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TABLE 15-continued

XRPD data of the Crystalline MeOH Solvate Form I of Compound 1 XRPD Peak Table	
Pos. [° 2 Th.]	Rel. Int. [%]
22.5	17.1
22.7	9.7
23.0	17.7
23.3	4.1
24.2	8.2
24.3	12.9
24.6	40.5
25.1	22.7
25.4	5.6
25.9	35.7
26.3	21.1
26.8	12.1
27.5	5.2
27.8	4.5
28.1	3.8
28.5	7.3
28.7	15.9
29.0	9.4
29.2	7.1
29.9	6.5
30.3	3.7
31.1	3.3
31.4	10.8
31.5	9.2
32.2	1.4
32.4	1.3
33.4	1.3
33.6	1.7
33.8	2.2
34.1	1.6
34.4	3.6
34.9	3.1
34.9	3.9
35.5	1.8
35.7	2.4
36.1	1.7
36.7	5.1
37.3	1.9
37.9	2.2
38.1	2.8
38.8	1.6
39.7	2.6
39.9	3.0

Example 16: Preparation of the Crystalline IPA
Solvate Form I of Compound 1

The crystalline isopropanol (IPA) solvate Form I of Compound 1 was prepared by slurry of amorphous Compound 1 in IPA at RT for 5 days.

The crystalline IPA solvate Form I of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 50), DSC (FIG. 51), and TGA (FIG. 52).

DSC endotherm onset of about 56° C., TGA comprising an approximate 8.7% weight loss when heated from about 39° C. to about 190° C. (0.9 mol IPA)

NMR 2.3 mol IPA

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.94 (d, J=6.62 Hz, 3H) 1.02-1.06 (m, 1H) 1.05 (d, J=5.98 Hz, 14H) 1.35 (d, J=6.62 Hz, 3H) 1.90 (s, 3H) 2.72 (br s, 1H) 3.10-3.21 (m, 1H) 3.45-3.58 (m, 1H) 3.78 (td, J=6.09, 4.06 Hz, 9H) 3.98-4.09 (m, 1H) 4.16 (br s, 1H) 4.35 (d, J=4.06 Hz, 8H) 4.91 (br d, J=0.85 Hz, 1H) 5.73-5.83 (m, 2H) 6.16-6.28 (m, 1H) 6.66-6.93 (m, 5H) 7.19 (dd, J=4.81, 0.75 Hz, 2H) 7.23-7.33 (m, 2H) 8.39 (d, J=4.92 Hz, 3H) 10.21 (br s, 1H).

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TABLE 16

XRPD data of the Crystalline MeOH Solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
7.1	84.1
9.2	73.8
9.8	47.9
10.2	4.2
10.6	89.1
11.2	17.2
11.7	5.1
13.7	38.9
14.1	82.0
14.6	7.5
14.8	1.8
16.6	90.0
16.8	30.3
17.2	20.0
17.5	52.1
18.0	23.3
18.2	15.9
18.6	38.1
18.8	100.0
18.9	75.5
19.2	10.6
19.7	52.3
20.4	27.0
21.0	21.5
21.3	65.6
22.0	28.6
22.2	14.3
22.5	50.5
22.9	19.9
23.1	27.1
23.3	8.6
23.5	8.8
23.8	11.3
24.2	19.0
24.8	12.0
25.0	16.1
25.4	37.9
25.5	45.3
26.1	16.0
26.6	5.6
27.0	11.0
27.7	15.1
27.8	8.3
28.2	8.7
28.5	10.5
28.7	18.2
29.0	2.9
29.3	2.6
29.5	6.7
29.9	9.8
30.2	6.2
30.4	7.9
30.9	4.5
31.2	5.0
31.7	4.2
31.8	4.8
32.7	3.4
32.9	6.2
33.0	5.8
33.5	6.0
34.1	5.5
34.7	2.3
35.2	3.0
35.5	0.8
35.9	2.1
36.2	2.5
36.5	4.4
36.6	3.5
36.9	2.7
37.0	2.6
37.4	5.7
38.1	1.2
38.3	1.0
38.7	1.2

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TABLE 16-continued

XRPD data of the Crystalline MeOH Solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
39.1	4.9
39.5	2.1

Example 17: Preparation of the Crystalline EtOH
Solvate Form I of Compound 1

The crystalline ethanol (EtOH) solvate Form I of Compound 1 was prepared by slurry of amorphous Compound 1 in EtOH at RT for 10 days.

The crystalline EtOH solvate Form I of Compound 1 prepared above was characterized by proton NMR, X-ray powder diffraction (XRPD) data (FIG. 53), DSC (FIG. 54), and TGA (FIG. 55).

DSC endotherm onset of about 194° C., TGA comprising an approximate 5% weight loss when heated from about 36° C. to about 195° C. (0.6 mol EtOH)

NMR 0.7 mol EtOH.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 0.84-1.02 (m, 5H) 1.02-1.12 (m, 5H) 1.35 (d, J=6.82 Hz, 3H) 1.90 (s, 3H) 2.52-2.77 (m, 1H) 3.14 (br t, J=10.87 Hz, 1H) 3.34-3.57 (m, 2H) 3.58-3.84 (m, 2H) 3.86-4.08 (m, 1H) 4.09-4.21 (m, 1H) 4.21-4.46 (m, 3H) 4.90 (br s, 1H) 5.51-5.80 (m, 1H) 6.20 (br dd, J=16.52, 4.58 Hz, 1H) 6.62-6.75 (m, 2H) 6.86 (dt, J=16.30, 11.24 Hz, 1H) 7.13-7.19 (m, 1H) 7.27 (td, J=8.20, 7.03 Hz, 1H) 8.16-8.36 (m, 2H) 8.39 (d, J=4.90 Hz, 1H) 10.20 (br s, 1H).

TABLE 17

XRPD data of the Crystalline EtOH Solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [°2 Th.]	Rel. Int. [%]
7.2	63.3
9.3	42.8
9.8	35.9
10.2	6.1
10.8	100.0
11.2	13.4
11.9	5.3
12.7	0.9
13.8	28.1
14.4	91.3
14.7	14.3
16.8	77.0
17.1	21.3
17.3	19.5
17.8	34.9
17.9	14.9
18.2	3.0
18.8	40.0
19.1	31.5
19.7	25.4
20.5	8.9
20.8	3.3
21.0	8.2
21.6	54.2
22.6	26.1
23.0	9.5
23.4	16.6
23.9	7.1
24.4	11.8
24.9	11.5
25.6	27.2

TABLE 17-continued

XRPD data of the Crystalline EtOH Solvate Form I of Compound 1 XRPD Peak Table:	
Pos. [$^{\circ}$ 2 Th.]	Rel. Int. [%]
25.7	24.1
26.2	5.4
26.5	14.6
27.3	8.6
27.8	8.2
28.7	11.6
29.0	7.1
29.3	1.6
29.9	4.9
30.3	1.8
30.5	3.0
31.0	6.1
31.3	2.3
31.8	2.1
32.3	1.7
32.7	0.1
33.5	2.4
34.1	4.1
34.7	1.7
35.0	1.6
35.7	1.1
36.5	1.3
37.1	4.8
38.0	3.2
39.5	1.4
39.8	1.8

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the disclosure. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

What is claimed is:

1. A compound, wherein the compound is a crystalline anhydrous form of the M atropisomer of 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-1-(4-methyl-2-(2-propenyl)-3-pyridinyl)-4-((2S)-2-methyl-4-(2-propenoyl)-1-piperazinyl)pyrido[2,3-d]pyrimidin-2(1H)-one (Compound 1) and wherein the compound is characterized by an x-ray powder diffraction pattern comprising a peak at 9.0 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

2. The compound of claim 1, wherein the compound is characterized by an x-ray powder diffraction pattern comprising a peak at 12.0 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

3. The compound of claim 1, wherein the compound is characterized by an x-ray powder diffraction pattern com-

prising a peak at 12.6 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

4. The compound of claim 2, wherein the compound is characterized by an x-ray powder diffraction pattern comprising a peak at 12.6 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

5. The compound of claim 1, wherein the compound is characterized by an x-ray powder diffraction pattern comprising a peak at 19.0 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

6. The compound of claim 2, wherein the compound is characterized by an x-ray powder diffraction pattern comprising a peak at 19.0 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

7. The compound of claim 3, wherein the compound is characterized by an x-ray powder diffraction pattern comprising a peak at 19.0 ± 0.2 degrees 2 theta as measured by using an x-ray wavelength of 1.54 Å.

8. A pharmaceutical composition comprising the compound of any one of claims 1-7 and a pharmaceutically acceptable excipient.

9. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition is a tablet.

10. The pharmaceutical composition of claim 9, wherein the tablet comprises 120 mg of the compound.

11. A method of treating cancer having a KRAS G12C mutation in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of the compound of any one of claims 1-7, wherein the cancer having a KRAS G12C mutation is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, liver cancer, small cell lung cancer, cervical cancer, germ cell tumor, ovarian cancer, pancreatic neuroendocrine tumor, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophageal cancer, soft tissue sarcoma, malignant mesothelioma, thyroid cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

12. The method of claim 11, wherein the cancer having a KRAS G12C mutation is non-small cell lung cancer, small intestine cancer, appendix cancer, colorectal cancer, endometrial cancer, pancreatic cancer, skin cancer, gastric cancer, nasal cavity cancer, or bile duct cancer.

13. The method of claim 11, wherein the cancer having a KRAS G12C mutation is non-small cell lung cancer or colorectal cancer.

14. The method of claim 11, wherein the cancer having a KRAS G12C mutation is pancreatic cancer or colorectal cancer.

15. The method of claim 11, wherein the compound is administered to an adult.

16. The method of claim 13, wherein the compound is administered to an adult.

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